



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/14, A61K 31/435, C07D 401/04, 205/04, 211/76		A1	(11) International Publication Number: WO 97/27185
			(43) International Publication Date: 31 July 1997 (31.07.97)
(21) International Application Number: PCT/EP97/00162		Sandra, Dora [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).	
(22) International Filing Date: 9 January 1997 (09.01.97)		(74) Agents: RUDDOCK, Keith, Stephen et al.; Pfizer Limited, European Patent Dept., Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).	
(30) Priority Data: 9601202.6 22 January 1996 (22.01.96) GB		(81) Designated States: AU, BG, BR, BY, CA, CN, CZ, HU, IL, IS, JP, KR, KZ, LK, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except GB JP US): PFIZER RESEARCH AND DEVELOPMENT COMPANY, N.V./S.A. [BE/IE]; La Touche House, International Financial Services Centre, Dublin 1 (IE).		Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(71) Applicant (for GB only): PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).			
(71) Applicant (for JP only): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): MACKENZIE, Alexander, Roderick [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). MARCHINGTON, Allan, Patrick [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). MIDDLETON, Donald, Stuart [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). MEADOWS,			
(54) Title: PIPERIDONE TACHYKININ ANTAGONISTS			
<div style="text-align: right;">(I)</div>			
(57) Abstract			
<p>The present invention provides compounds of formula (I) and the pharmaceutically acceptable acid addition salts thereof, wherein X is a direct link or C₁-C₄ alkylene; and R is C₃-C₇ cycloalkyl optionally substituted by 1 or 2 substituents each independently selected from fluoro and C₃-C₇ cycloalkyl: with the proviso that X is not methylene when R is cyclopropyl, together with processes for the preparation of, intermediates used in the preparation of, compositions containing and uses of, such compounds. These compounds are useful as tachykinin antagonists.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

PIPERIDONE TACHYKININ ANTAGONISTS

5 This invention relates to piperidones. More particularly, this invention relates to 5-(3,4-dichlorophenyl)-5-(2-[3-(4-fluoropiperidin-1-yl)]azetidin-1-yl)ethylpiperidin-2-one derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and uses of, such derivatives.

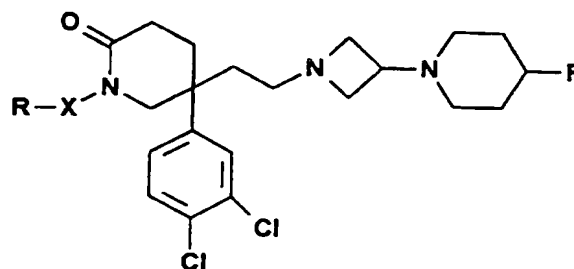
10 These derivatives are antagonists of tachykinins, including NKA, NKB and Substance P, acting at the human neurokinin-1 (NK₁), neurokinin-2 (NK₂) or neurokinin-3 (NK₃) receptor, or any combination thereof. The derivatives are therefore useful for preventing or treating an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous
15 system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a disease caused by Helicobacter pylori or other urease-positive Gram negative bacteria, an urogenital tract disorder such as incontinence, impotence,
20 hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a vasospastic disease such as angina or Reynaud's disease, a fibrosing or collagen disease such as scleroderma or eosinophilic fasciitis, reflux sympathetic dystrophy such as shoulder/hand
25 syndrome, an addiction disorder such as alcoholism, a stress-related somatic disorder, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, a neuropathological disorder such as Alzheimer's disease or multiple sclerosis, a disorder related to immune enhancement or suppression such as
30 systemic lupus erythematosus, a rheumatic disease such as fibrositis, emesis, cough, acute or chronic pain, migraine, or an ophthalmic disease such as proliferative retinopathy.

These derivatives are particularly potent and selective antagonists of tachykinins, including NKA, NKB and Substance P, acting at the human NK₂

receptor. They are particularly useful for treating or preventing an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, an urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain.

International Patent Application Publication no. WO96/05193 discloses azetidinyllactam derivatives with tachykinin antagonist activity, including 1-cyclopropylmethyl-5-(3,4-dichlorophenyl)-5-(2-[3-(4-fluoropiperidin-1-yl)]azetidin-1-yl)ethylpiperidin-2-one and pharmaceutically acceptable salts thereof.

The present invention provides a compound of the formula:-



(I)

or a pharmaceutically acceptable acid addition salt thereof,

wherein X is a direct link or C₁-C₄ alkylene; and

R is C₃-C₇ cycloalkyl optionally substituted by 1 or 2 substituents each independently selected from fluoro and C₃-C₇ cycloalkyl; with the proviso that X is not methylene when R is cyclopropyl.

In the above definition of a compound of the formula (I), an alkylene group containing 3 or 4 carbon atoms may be straight- or branched-chain.

5 Preferably, X is a direct link, methylene or ethylene.

Most preferably, X is methylene.

10 Preferably, R is C₃-C₆ cycloalkyl optionally substituted by 1 or 2 substituents each independently selected from fluoro and C₃-C₆ cycloalkyl, preferably cyclopropyl.

More preferably, R is cyclopropyl, 1-cyclopropylcyclopent-1-yl, cyclohexyl or 4,4-difluorocyclohexyl.

Most preferably, R is 4,4-difluorocyclohexyl.

15 Suitable acid addition salts are formed from acids which form non-toxic salts and examples include the hydrochloride, hydrobromide, hydroiodide, sulphate, hydrogen sulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, benzoate, methanesulphonate, benzenesulphonate, p-toluenesulphonate, 5-sulphosalicylate
20 and 10-camphorsulphonate salts. A preferred acid addition salt is the disuccinate salt.

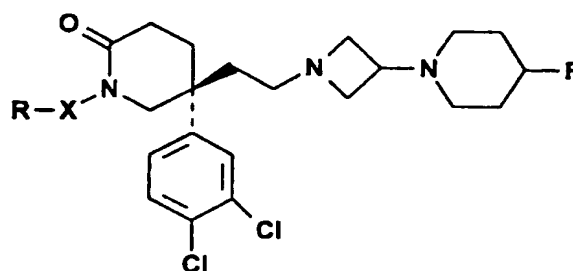
For a review on suitable acid addition salts see Berge et al, J. Pharm. Sci., 66, 1-19 (1977).

25 A compound of the formula (I) contains at least one asymmetric carbon atom and therefore exists in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) and mixtures thereof.

30 Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may

also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed
 5 by reaction of the corresponding racemate with a suitable optically active acid.

The preferred compounds of the formula (I) have the (S)- stereochemistry at the 5-position of attachment of the 3,4-dichlorophenyl and 2-[3-(4-fluoropiperidin-1-yl)]azetidin-1-ylethyl groups to the piperidin-2-one ring, i.e.



(IA)

10 wherein X and R are as previously defined for a compound of the formula (I).

Preferred examples of a compound of the formula (I) are those wherein:

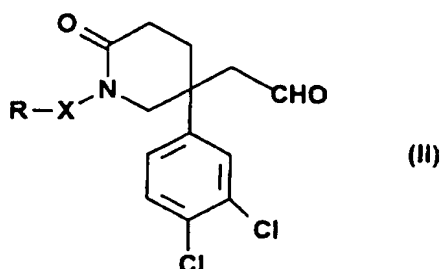
- (i) R-X- is 4,4-difluorocyclohexylmethyl;
- (ii) R-X- is cyclohexyl;
- 15 (iii) R-X- is 1-cyclopropylcyclopent-1-yl; or
- (iv) R-X- is 2-cyclopropylethyl;

or any such compound with the (S)- stereochemistry at the 5-position of the 2-piperidinone ring, or a pharmaceutically acceptable acid addition salt of any thereof.

20 A particularly preferred compound of the formula (I) is 5(S)-5-(3,4-dichlorophenyl)-1-(4,4-difluorocyclohexylmethyl)-5-(2-[3-(4-fluoropiperidin-1-yl)]azetidin-1-yl)ethylpiperidin-2-one or an acid addition salt thereof and preferably a disuccinate salt thereof.

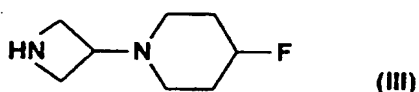
The compounds of the formula (I) provided by the invention can be
 25 prepared by the following methods:

1) The compounds of the formula (I) can be prepared by reductive amination using as starting materials a compound of the formula:-



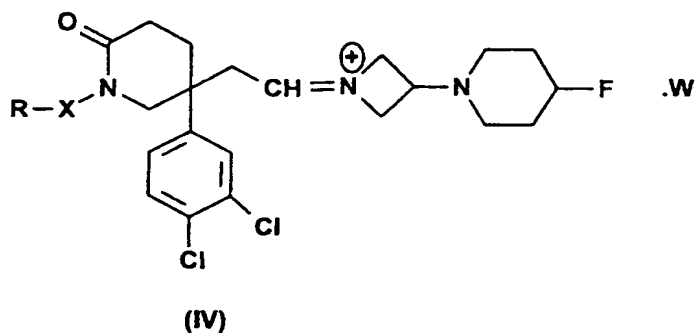
5

where R and X are as previously defined for a compound of the formula (I), and a compound of the formula:-



, or an acid addition salt thereof. The reaction is preferably carried out in the presence of a suitable acid, e.g. acetic acid.

The reaction proceeds via the initial formation of an intermediate iminium salt of the formula:-



where W is an anion (e.g. acetate) derived from a suitable acid (e.g. acetic acid), which may be stable and isolatable. The reaction is preferably carried out without isolation of the intermediate of the formula (IV), in which case it is reduced in situ to provide a compound of formula (I).

In a typical procedure, an aldehyde of the formula (II) is first reacted with an azetidine of the formula (III) in a suitable solvent, e.g. tetrahydrofuran, and the mixture is then treated with a suitable reducing agent, e.g. sodium triacetoxyborohydride or sodium cyanoborohydride, in the presence of a suitable

acid, e.g. acetic acid, to give the required product. If an acid addition salt of an azetidine of the formula (III) is used as a starting material, a suitable acid acceptor, e.g. triethylamine, is preferably added prior to the addition of the
5 reducing agent.

3-(4-Fluoropiperidin-1-yl)azetidine dihydrochloride or toluenesulphonate (tosylate) is a preferred starting material for this method.

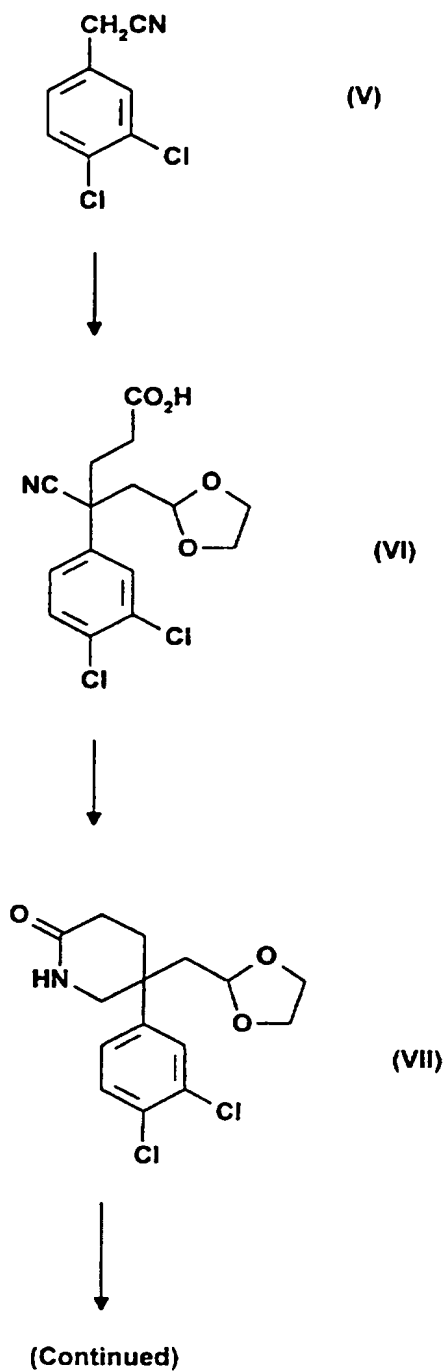
The reaction is typically carried out at room temperature.

The compounds of the formula (III) can be prepared by conventional
10 procedures.

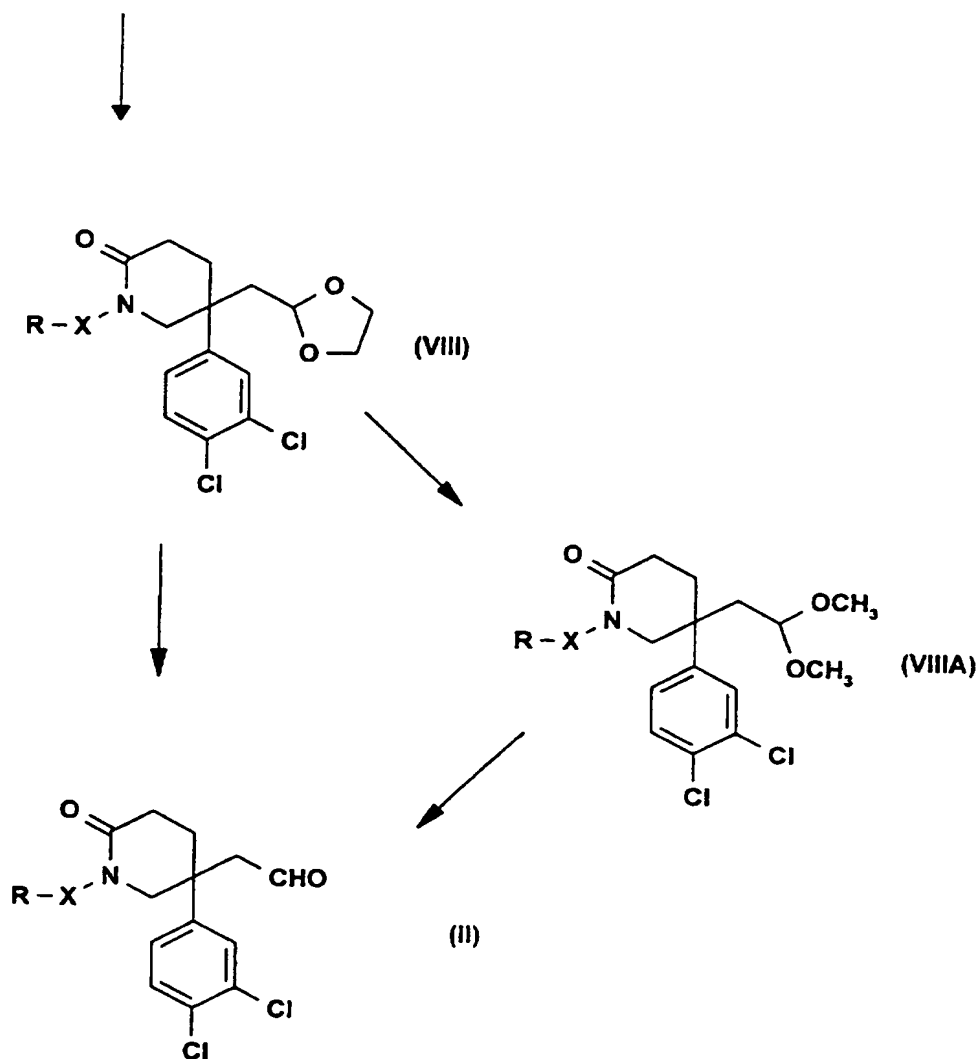
The aldehydes of the formula (II) can be prepared by the method shown in Scheme 1:-

Scheme 1

5

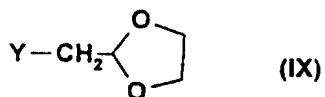


(Continued)

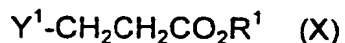


wherein R and X are as previously defined for a compound of the formula (I).

- 5 In a typical procedure, the compound of the formula (V) is first deprotonated with approximately one mole equivalent of a suitable base, e.g. lithium hexamethyldisilylazide, and in a suitable aprotic organic solvent, e.g. tetrahydrofuran, and then reacted with a compound of the formula:



wherein Y is a suitable leaving group, e.g. bromo, optionally in the presence of a suitable catalyst, e.g. tetra-n-butylammonium iodide. The alkylated compound produced is then deprotonated with approximately one equivalent of a suitable
5 base, e.g. lithium hexamethyldisilylazide, and in a suitable aprotic organic solvent, e.g. tetrahydrofuran, and then further alkylated with a compound of the formula:



10 wherein Y^1 is a suitable leaving group, e.g. halo, preferably chloro, bromo or iodo, methanesulphonyloxy, trifluoromethanesulphonyloxy or para-toluenesulphonyloxy, and R^1 is C_1 - C_4 alkyl, preferably methyl or ethyl. The ester produced can then be hydrolysed to the corresponding carboxylic acid of the formula (VI) under conventional conditions, e.g. using a suitable aqueous mineral acid or base,
15 preferably sodium hydroxide.

The alkylation with the compound of the formula (X) can be carried out in situ, i.e. without isolating the alkylated compound produced by the reaction of the compounds of the formula (V) and (IX). The ester produced also does not need to be isolated and can be hydrolysed to the carboxylic acid of the formula (VI) in the
20 work-up procedure.

If desired, the (R) and (S) enantiomers of the compound of the formula (VI) may be separated by reaction of the carboxylic acid of the formula (VI) with a suitable optically active base, e.g. (R)-(+)- or (S)-(-)-alpha-methylbenzylamine, followed by isolation of the desired optically pure enantiomer(s) using conventional
25 procedures.

Preferably, (S)-(-)-alpha-methylbenzylamine is used for the resolution and the salt obtained is not converted to the free acid of the formula (VI) but is used directly in the next cyclisation step.

The compound of the formula (VI) is converted to the piperidin-2-one of the
30 formula (VII) by reductive cyclisation using a suitable catalyst, e.g. platinum oxide, under acidic conditions, e.g. using acetic acid as the solvent, under an atmosphere of hydrogen.

The piperidin-2-one of the formula (VII) can then be N-alkylated with a compound of the formula:



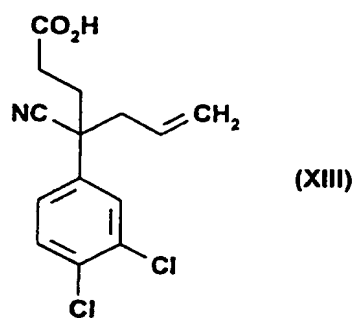
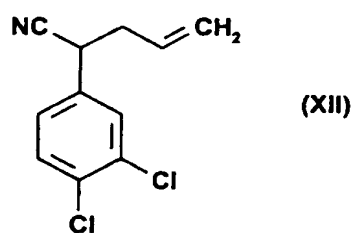
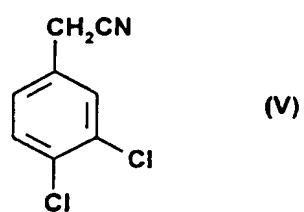
wherein R and X are as previously defined for a compound of the formula (I) and Y^2 is a suitable leaving group, e.g. halo, preferably chloro, bromo or iodo, methanesulphonyloxy or para-toluenesulphonyloxy, in the presence of a suitable
10 base, e.g. potassium hydroxide, and in a suitable solvent, e.g. dimethyl sulphoxide, to provide a compound of the formula (VIII).

A compound of the formula (VIII) can be directly converted to an aldehyde of the formula (II) by acidic hydrolysis, e.g. using aqueous hydrochloric acid, in the presence of a suitable solvent, e.g. tetrahydrofuran.

15 Alternatively, a compound of the formula (VIII) can be first converted to a dimethyl acetal of the formula (VIII A) by treatment with a suitable acidic ion exchange resin, e.g. AMBERLYST 15 (trade mark), in a suitable solvent, e.g. methanol. The acetal can then be converted to an aldehyde of the formula (II) by treatment with a suitable acid, e.g. aqueous hydrochloric acid, in the presence of a
20 suitable solvent, e.g. tetrahydrofuran.

The compounds of the formula (XI) used in this method may be prepared by conventional procedures.

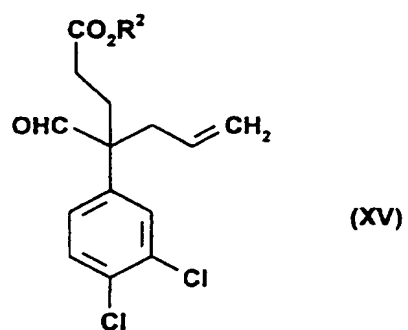
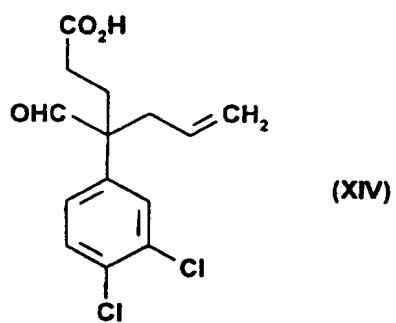
The aldehydes of the formula (II) can also be prepared by the method shown in Scheme 2:

Scheme 2

(Continued)

12

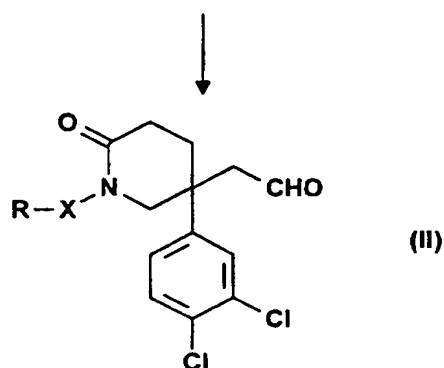
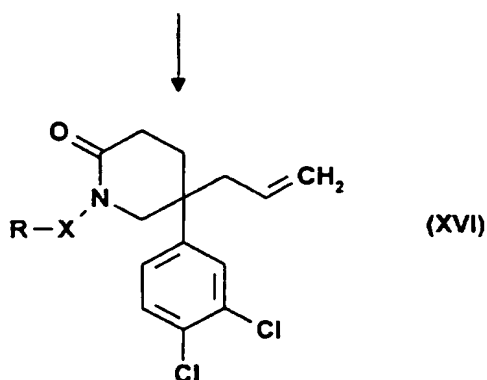
(Continued)



↓

(Continued)

(Continued)



- 5 wherein R and X are as previously defined for a compound of the formula (I) and R^2 is C_1 - C_4 alkyl, preferably methyl or ethyl.

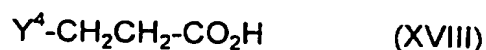
In a typical procedure, a compound of the formula (V) is first deprotonated with a suitable base and then alkylated with a compound of the formula:-



- wherein Y^3 is a suitable leaving group, e.g. halo, preferably, bromo, methanesulphonyloxy or p-toluenesulphonyloxy. The reaction is preferably carried out by first deprotonating a compound of the formula (V) using an aqueous solution of sodium hydroxide in the presence of a suitable organic solvent, e.g.
- 15 cyclohexane, followed by alkylation using allyl bromide in the presence of a phase

transfer catalyst, preferably tetra-n-butylammonium chloride.

The compound of the formula (XII) prepared is then first deprotonated with a suitable base, e.g. sodium hydride, and then alkylated with a base salt of a
5 compound of the formula:



wherein Y^4 is a suitable leaving group, e.g. halo, preferably chloro or bromo, the
10 reaction being carried out in a suitable aprotic organic solvent, e.g. tetrahydrofuran. Treatment with acid in the work-up procedure provides the desired carboxylic acid. Preferably, a sodium salt of a compound of the formula (XVIII) is used.

If desired, the (R) and (S) enantiomers of the compound of the formula
15 (XIII) prepared may be separated by reaction of the compound of the formula (XIII) with a suitable optically active base, e.g. R-(+)- or (S)-(-)-1-(1-naphthyl)ethylamine, followed by isolation of the desired optically active enantiomer(s) using conventional procedures.

The compound of the formula (XIII) can be converted to an aldehyde of the
20 formula (XIV) by reduction using a suitable reducing agent, e.g. diisobutylaluminium hydride, in a suitable organic solvent, e.g. toluene, followed by hydrolysis of the intermediate complex with an aqueous solution of a suitable acid, e.g. citric acid.

Esterification of the compound of the formula (XIV) can be achieved using
25 conventional conditions, e.g. by first forming an activated ester derivative using 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide using dichloromethane as solvent, followed by the addition of a C_1-C_4 alkanol (i.e. a compound of the formula R^2OH).

Reductive amination of a compound of the formula (XV) using a compound
30 of the formula:



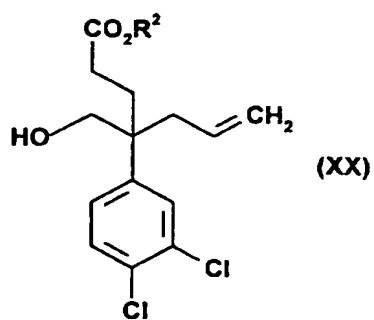
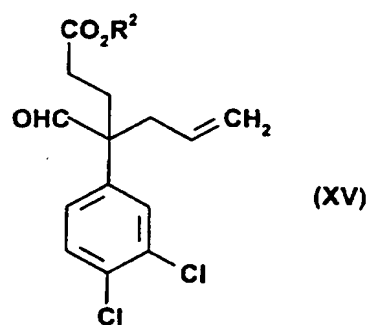
, wherein R and X are as previously defined for a compound of the formula (I), in the presence of a suitable reducing agent, e.g. sodium triacetoxyborohydride, and a suitable acid, e.g. acetic acid, and in a suitable solvent, e.g. tetrahydrofuran, provides an intermediate secondary amine that can be cyclised in situ to give a piperidone of the formula (XVI).

A piperidone of the formula (XVI) can be converted to an aldehyde of the formula (II) using a conventional ozonolysis technique.

The compounds of the formula (XIX) used in this method can be prepared by conventional procedures.

An alternative method for converting a compound of the formula (XV) to a compound of the formula (XVI) is shown in Scheme 3:

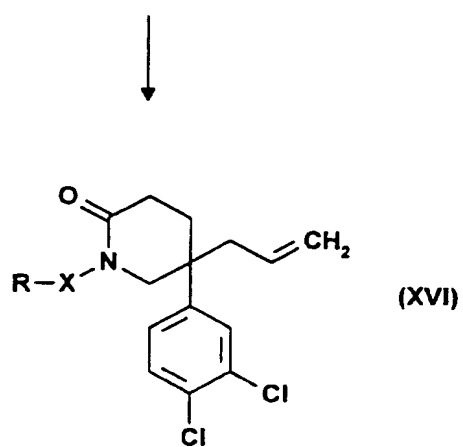
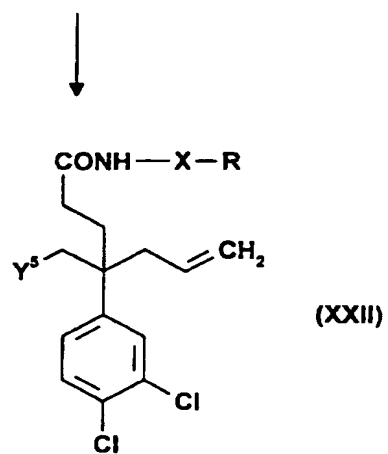
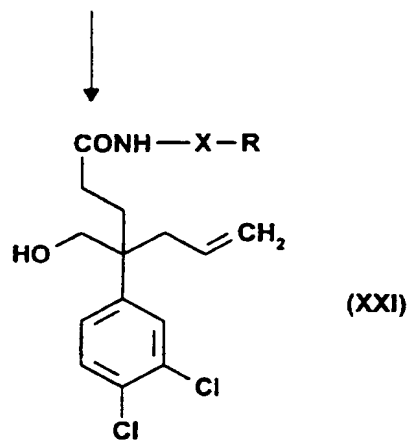
16

Scheme 3

(Continued)

17

(Continued)



wherein R and X are as previously defined for a compound of the formula (I), R² is C₁-C₄ alkyl, preferably methyl or ethyl, and Y⁵ is a suitable leaving group, e.g. methanesulphonyloxy or para-toluenesulphonyloxy.

- 5 In a typical procedure, an aldehyde of the formula (XV) is reduced to a alcohol of the formula (XX) using a suitable reducing agent, e.g. sodium triacetoxyborohydride, in a suitable solvent, e.g. tetrahydrofuran, and in the presence of a suitable acid, e.g. acetic acid.

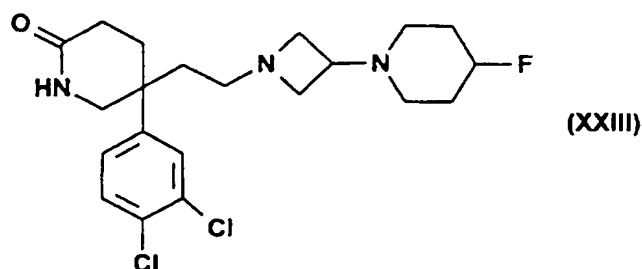
- 10 An ester of the formula (XX) can be converted to an amide of the formula (XXI) under conventional conditions such as by reaction with a compound of the formula (XIX) at an elevated temperature, optionally in the presence of a suitable solvent, e.g. toluene or dimethylformamide.

- Conventional functional group interconversion of a compound of the formula (XXI) can provide a compound of the formula (XXII). For example, to
15 obtain a compound of the formula (XXII) where Y⁵ is methanesulphonyloxy, a compound of the formula (XXI) is reacted with methanesulphonyl chloride in the presence of a suitable acid acceptor, e.g. triethylamine, and in a suitable solvent, e.g. dichloromethane.

- A compound of the formula (XXII) is then first N-deprotonated using a
20 suitable base, e.g. sodium hydride, and then cyclised *in situ* to provide a piperidone of the formula (XVI), the reaction being carried out in a suitable solvent, e.g. tetrahydrofuran.

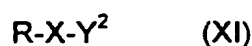
- Further methods for the preparation of the aldehydes of the formula (II) are described in International Patent Application Publication no. WO96/05193, the
25 teaching of which is incorporated herein by reference in this respect.

- 2) The compounds of the formula (I) can be prepared by alkylation of a N-deprotonated form of a compound of the formula:



with a compound of the formula:

5



wherein R, X and Y² are as previously defined for a compound of the formula (XI).

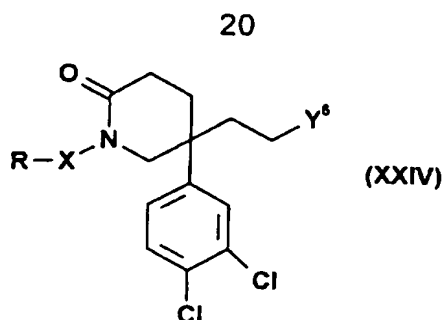
In a typical procedure, a compound of the formula (XXIII) is first
 10 deprotonated with a suitable base, e.g. sodium hydride, and then alkylated in situ
 with a compound of the formula (XI) where Y² is preferably bromo or
 methanesulphonyloxy. The reaction is typically carried out in a suitable solvent,
 e.g. dimethylformamide.

Alternatively, the reaction can be carried out by reacting the starting
 15 materials of the formulae (XXIII) and (XI) together in the presence of a suitable
 base, e.g. potassium hydroxide, and in a suitable solvent, e.g. dimethylsulphoxide,
 at about room temperature. If a compound of the formula (XI) where Y² is chloro
 is used, potassium iodide may also be added to increase the rate of reaction.

The starting materials of the formula (XXIII) can be prepared by
 20 conventional methods such as by adaptation of the preparation described in
 Method (1), Scheme 1, to convert a compound of the formula (VII) directly to the
 corresponding aldehyde, followed by reductive amination thereof with a compound
 of the formula (III), or an acid addition salt thereof, by the procedure of Method (1).

The starting compounds of the formula (XI) can be prepared by
 25 conventional methods.

3) The compounds of the formula (I) can be prepared by reaction of a
 compound of the formula:



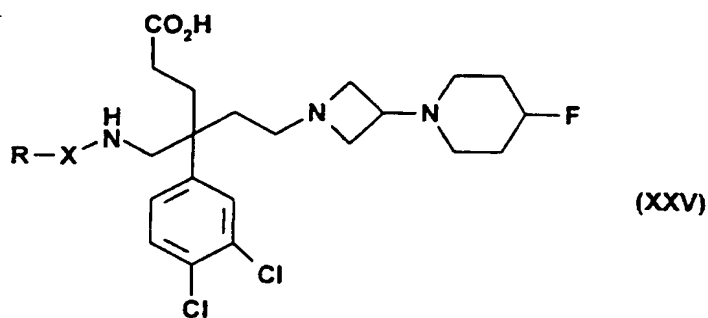
wherein R and X are as previously defined for a compound of the formula (I) and
 5 Y⁶ is a suitable leaving group, e.g. chloro, bromo, iodo, methanesulphonyloxy, trifluoromethanesulphonyloxy or p-toluenesulphonyloxy, with a compound of the formula (III). The compound of the formula (III) may be generated *in situ* from an acid addition salt thereof using a suitable acid acceptor.

In a typical procedure, a compound of the formula (XXIV) is reacted with a
 10 compound of the formula (III), or an acid addition salt thereof, in the presence of a suitable acid acceptor, e.g. triethylamine or potassium carbonate, in a suitable solvent, e.g. acetonitrile.

The starting materials of the formula (XXIV) can be prepared by first
 reducing the aldehydes of the formula (II) to the corresponding primary alcohols,
 15 then converting the hydroxy group thereof to the required leaving group Y⁶ using conventional conditions.

4) The compounds of the formula (I) can be prepared by intramolecular dehydration of a compound of the formula:

20

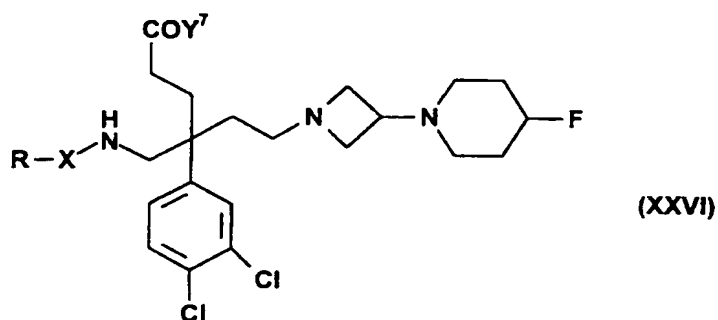


wherein R and X are as previously defined for a compound of the formula (I).

In a typical procedure, the dehydration is carried out under Dean-Stark conditions in a suitable solvent, e.g. toluene, and in the presence of a suitable acid, e.g. p-toluenesulphonic acid. Alternatively, the dehydration can be carried out by stirring a solution of a compound of the formula (XXV) in a suitable solvent, e.g. dichloromethane, in the presence of a dehydrating agent such as silica gel.

The starting materials of the formula (XXV) can be prepared by conventional methods.

5) The compounds of the formula (I) can be prepared by intramolecular cyclisation of a compound of the formula:



wherein R and X are as previously defined for a compound of the formula (I) and Y^7 is a suitable leaving group, e.g. C_1 - C_4 alkoxy, benzyloxy, imidazol-1-yl or benzotriazol-1-yloxy.

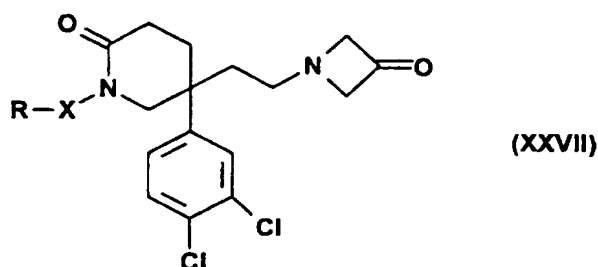
In typical procedures:

- (i) where Y^7 is C_1 - C_4 alkoxy or benzyloxy, a solution of a compound of the formula (XXVI) in a suitable solvent, e.g. methanol or ethanol, is heated at about the reflux temperature of the solvent;
- (ii) where Y^7 is imidazol-1-yl, a compound of the formula (XXVI) is obtained by reacting a compound of the formula (XXV) with 1,1'-carbonyldiimidazole in a suitable solvent, e.g. dichloromethane, and in situ cyclisation of the intermediate imidazolid provides the required product; and

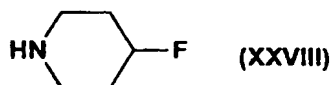
- (iii) where Y⁷ is benzotriazol-1-yloxy, a compound of the formula (XXVI) is derived in situ by reacting a compound of the formula (XXV) with 1-hydroxybenzotriazole in the presence of a suitable dehydrating agent, e.g. 1,3-dicyclohexylcarbodiimide, and in a suitable solvent, e.g. dichloromethane, and in situ cyclisation of the intermediate activated ester provides the required product.

The starting materials of the formula (XXVI) can be prepared by conventional methods such as from a compound of the formula (XXV), examples of which are described above.

- 6) The compounds of the formula (I) can be prepared by reductive amination using as starting materials a compound of the formula:

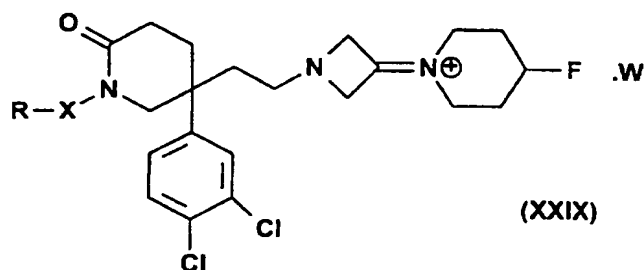


wherein R and X are as previously defined for a compound of the formula (I), and a compound of the formula:



, or an acid addition salt thereof. The reaction is preferably carried out in the presence of a suitable acid, e.g. acetic acid. The reaction is typically carried out using a similar procedure to that described in Method (1). The reaction proceeds via an intermediate iminium salt of the formula:

23

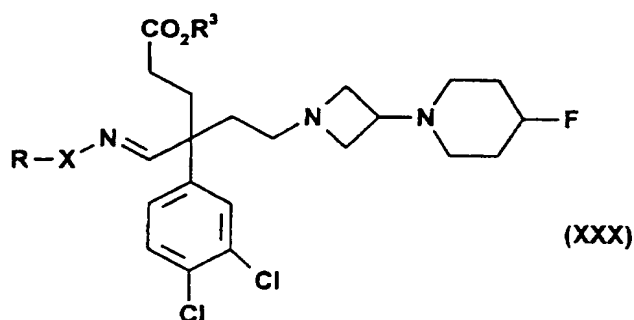


- 5 wherein W is an anion (e.g. acetate) derived from a suitable acid (e.g. acetic acid) and R and X are as previously defined for a compound of the formula (I), which may be stable and isolatable.

The reaction is preferably carried out without isolation of a compound of the formula (XXIX) in which case it is reduced in situ to provide a compound of the
10 formula (I).

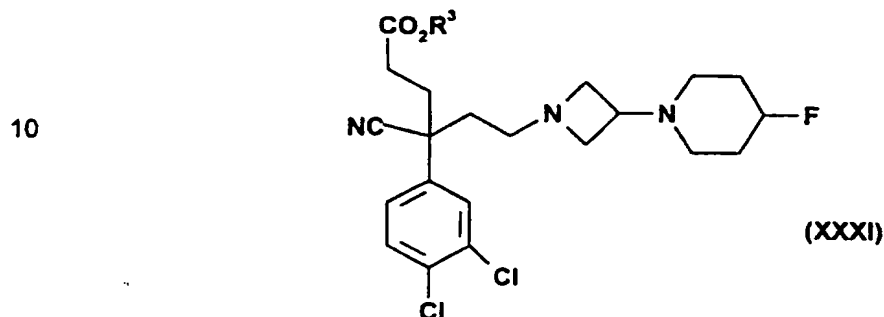
The starting materials of the formula (XXVII) may be prepared by oxidation of the corresponding azetidin-3-ol derivatives (which can be prepared by reaction of a compound of the formula (XXIV) with azetidin-3-ol using a conventional procedure) using standard conditions, e.g. using pyridinium chlorochromate or
15 tetrapropylammonium perruthenate as the oxidising agent.

- 7) The compounds of the formula (I) can be prepared by reductive cyclisation of a compound of the formula:



wherein R and X are as previously defined for a compound of the formula (I) and R^3 is a suitable ester-forming group, e.g. C_1 - C_4 alkyl, preferably methyl or ethyl, or benzyl.

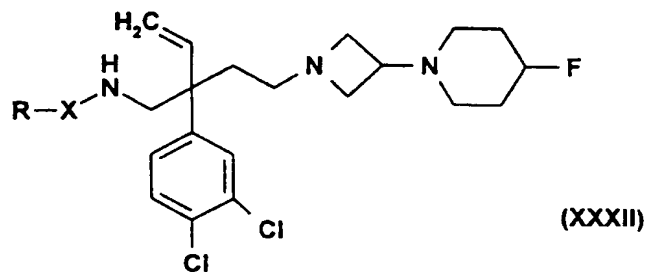
- 5 In a typical procedure, a compound of the formula (XXX) is first generated in situ by reacting a compound of the formula:



- 15 wherein R^3 is as previously defined for a compound of the formula (XXX) with a compound of the formula (XIX) wherein R and X are as previously defined for a compound of the formula (I), and then the reductive cyclisation is facilitated by the presence of a suitable reducing agent, e.g. Raney nickel. The reaction is carried out in a suitable solvent, e.g. methanol or ethanol, and under an atmosphere of
- 20 hydrogen.

The starting materials of the formula (XXXI) can be prepared by conventional methods.

- 8) The compounds of the formula (I) can be prepared by catalysed carbonyl
- 25 addition-cyclisation of a compound of the formula:

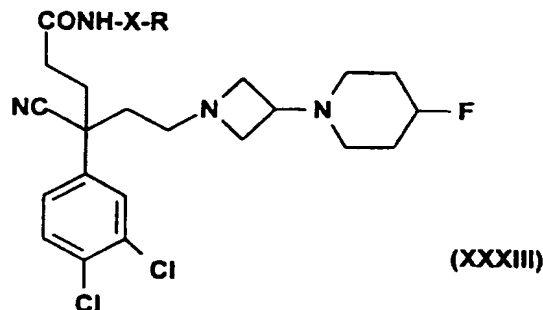


wherein R and X are as previously defined for a compound of the formula (I).

The reaction is typically carried out under an atmosphere of carbon monoxide using a suitable catalyst, e.g. tetrakis(triphenylphosphine)palladium (O), a
 5 suitable base, e.g. triethylamine, and in a suitable organic solvent, e.g. tetrahydrofuran, at about room temperature.

The compounds of the formula (XXXII) may be prepared by conventional methods.

- 10 9) The compounds of the formula (I) can be prepared by reductive cyclisation of a compound of the formula:



- 15 wherein X and R are as previously defined for a compound of the formula (I).

In a typical procedure, the reductive cyclisation is carried out using a suitable catalyst, e.g. platinum oxide, under a hydrogen atmosphere and in a suitable solvent, e.g. acetic acid, at room temperature and 414 kPa (60 p.s.i.).

- 20 The compounds of the formula (XXXIII) may be generated by conventional procedures such as from a compound of the formula (XXXI).

All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well known to those skilled in the art with
 25 reference to literature precedents and the Examples and Preparations hereto.

A pharmaceutically acceptable acid addition salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of

the formula (I) and the desired acid. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

The affinity of the compounds of formula (I) and their salts for the human NK₁ receptor can be tested *in vitro* by testing their ability to inhibit [³H]-Substance P binding to membranes prepared from the human IM9 cell line expressing the human NK₁ receptor using a modification of the method described in McLean, S. *et al*, J. Pharm. Exp. Ther., **267**, 472-9 (1993) in which whole cells were used.

The affinity of the compounds of formula (I) and their salts for the human NK₂ receptor can be tested *in vitro* by testing their ability to compete with [³H] or [¹²⁵I]NKA (neurokinin A) for binding to membranes prepared from Chinese hamster ovary cells expressing the cloned human NK₂ receptor. In this method, washed Chinese hamster ovary cell membranes are prepared as described for the previous method where IM9 cells are used instead. The membranes are incubated (90 min, 25°C) with [³H] or [¹²⁵I]NKA and with a range of concentrations of the test compound. Non-specific binding was determined in the presence of 10µM NKA.

The NK₂ receptor antagonist activity of the compounds of the formula (I) can be tested, *in vitro*, by testing their ability to antagonise the contractile effects of the selective NK₂ receptor agonist [βAla⁸]NKA₍₄₋₁₀₎ in the rabbit pulmonary artery, using the method of Patacchini and Maggi, Eur. J. Pharmacol., **236**, 31-37 (1993).

The compounds of the formula (I) and their salts can be tested for NK₂ receptor antagonist activity, *in vivo*, by testing their ability to inhibit bronchoconstriction induced by [βAla⁸]NKA₍₄₋₁₀₎ in the anaesthetised guinea pig, using the method described by Murai *et al*, J. Pharm. Exp. Ther., **262**, 403-408 (1992) or Metcalfe *et al*, Br. J. Pharmacol., **112**, 563P (1994).

The compounds of the formula (I) and their salts can be tested for NK₃ receptor antagonist activity, *in vitro*, by testing their ability to antagonise the contractile effects of the selective NK₃ receptor agonist senktide in the guinea pig ileum using the method of Maggi *et al*, Br. J. Pharmacol., **101**, 996-1000 (1990).

For human use, the compounds of the formula (I) and their salts can be administered alone, but will generally be administered in admixture with a pharmaceutically acceptable diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally, including sublingually and buccally, in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents. They can be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) and their salts will be from 0.001 to 20, preferably from 0.01 to 20, and most preferably from 0.1 to 10, mg/kg (in single or divided doses). Thus tablets or capsules of the compounds will contain from 0.1 to 500, preferably from 10 to 200, mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Alternatively, the compounds of the formula (I) can be administered intranasally, by inhalation or in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. An alternative means of transdermal administration is by use of a skin patch. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin, or they can be incorporated, at a concentration of between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers

and preservatives as may be required. The compounds of the formula (I) may also be administered in the form of an aerosol spray presentation or by using a dry powder inhaler formulation.

5 It is to be appreciated that reference to treatment includes prophylaxis as well as the alleviation of established symptoms of the disease.

Thus the invention further provides:-

- (i) a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier;
- (ii) a compound of the formula (I), or a pharmaceutically acceptable acid addition salt or composition thereof, for use as a medicament;
- (iii) the use of a compound of the formula (I), or of a pharmaceutically acceptable acid addition salt or composition thereof, for the manufacture of a medicament for the treatment of a disease by producing an antagonist effect on a tachykinin acting at the human NK₁, NK₂ or NK₃ receptor, or any combination thereof;
- (iv) use as in (iii) where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, an urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain;
- (v) a method of treatment of a human to treat a disease by producing an antagonist effect on a tachykinin acting at the human NK₁, NK₂ or NK₃

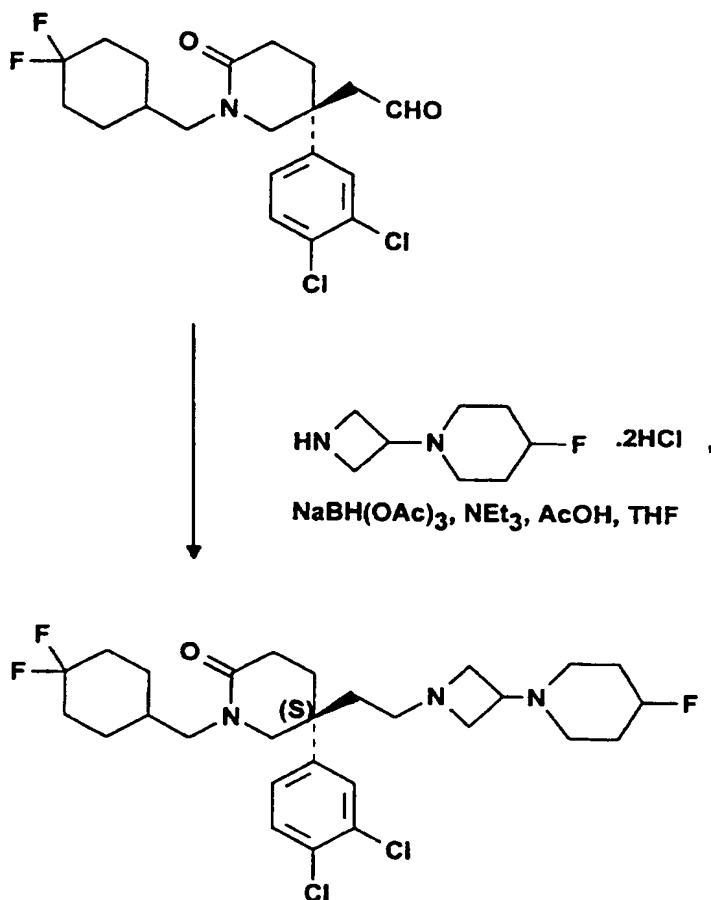
receptor, or any combination thereof, which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable acid addition salt or composition thereof;

- 5 (vi) a method as in (v) where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal
10 incontinence, colitis or Crohn's disease, an urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful
15 neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain; and
- (vii) a compound of the formula (IV), (VIII A), (XXIII), (XXV), (XXVI), (XXVII), (XXIX), (XXX), (XXXI), (XXXII) or (XXXIII) or a para-toluenesulphonate salt of a compound of the formula (III).
- 20

The following Examples illustrate the preparation of the compounds of the formula (I):-

EXAMPLE 1

- 5 5(S)-5-(3,4-Dichlorophenyl)-1-(4,4-difluorocyclohexylmethyl)-5-(2-[3-(4-fluoropiperidin-1-yl)]azetidin-1-yl)ethylpiperidin-2-one



- To a solution of the aldehyde (see Preparations 1 and 15) (125 mg, 0.299 mmol) and 3-(4-fluoropiperidin-1-yl)azetidine dihydrochloride (see Preparation 3) (70 mg, 1.01 mol equiv.) in tetrahydrofuran (8 ml) under nitrogen was added triethylamine (0.092 ml, 2.2 mol equiv.). After stirring for one hour, sodium triacetoxyborohydride (0.095 g, 1.5 mol equiv.) was added followed by glacial acetic acid (0.017 ml, 1 mol equiv.) and the mixture was stirred for 18 hours. The solvent was removed by evaporation under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate solution (20 ml) and ethyl acetate (20 ml). The aqueous portion was separated and further

extracted with ethyl acetate (2 x 20 ml). The organic layers were then combined and dried over sodium sulphate. The mixture was filtered and the solvent removed from the filtrate by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with methanol:dichloromethane (2:25, by volume) to provide the title compound (103 mg). TLC R_f = 0.18 (silica, methanol:dichloromethane, 1:19, by volume). LRMS 561.7 (m+1)⁺.

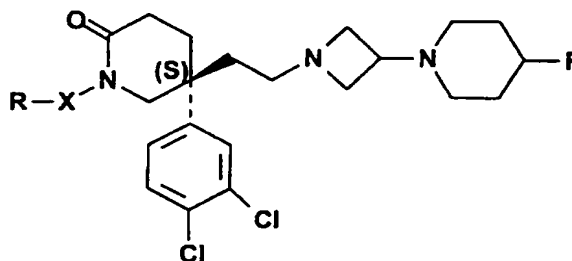
Found: C, 59.49; H, 6.81; N, 7.38. C₂₈H₃₈N₃OF₃Cl₂. 0.625 CH₂Cl₂ requires C, 59.56; H, 6.79; N, 7.43%.

¹H-NMR (CDCl₃): δ = 1.2-1.45 (m, 2H), 1.5-2.25 (m, 19H), 2.3-2.5 (m, 3H), 2.6-2.8 (m, 2H), 2.85-3.0 (m, 1H), 3.15-3.25 (m, 1H), 3.3-3.5 (m, 4H), 3.5-3.6 (m, 2H), 4.5-4.8 (m, 1H), 7.0-7.1 (m, 1H), 7.2-7.5 (m, 2H) ppm.

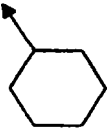


[α]_D²⁵ = -28° (c = 0.001 in methanol, cell length = 1 decimetre).

EXAMPLES 2 to 4

The compounds of the following tabulated Examples of the general formula:



were prepared by a similar method to that of Example 1 using the appropriate aldehyde starting materials (see Preparations 2, 7 and 8).

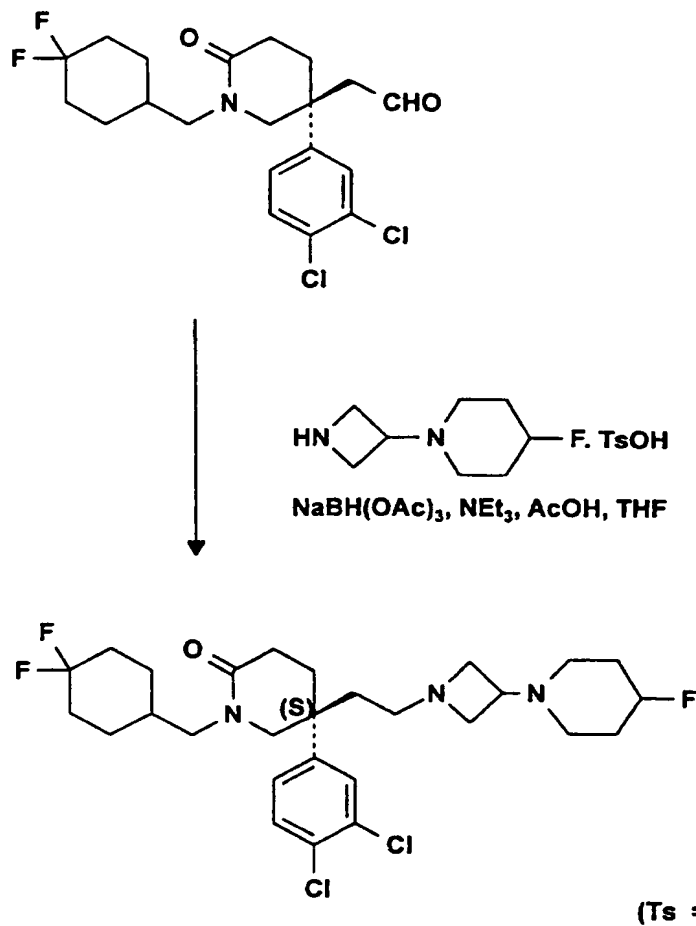
EXAMPLE NO.	R-X-	LRMS	¹ H-NMR
2 ¹		510 (m) ⁺	¹ H-NMR (CDCl ₃): δ = 1.0-2.3 (m, 23H), 2.3-2.5 (m, 3H), 2.6-2.8 (m, 2H), 2.8-3.0 (m, 1H), 3.1-3.2 (m, 1H), 3.3-3.6 (m, 3H), 4.4-4.8 (m, 2H), 7.05-7.15 (m, 1H), 7.3-7.45 (m, 2H) ppm.
3 ²		-	¹ H-NMR (CDCl ₃): δ = 0.4-0.6 (m, 4H), 1.4-1.6 (m, 1H), 1.8-2.3 (m, 23H), 2.3-2.5 (m, 2H), 2.6-2.8 (m, 1H), 2.8-3.0 (m, 1H), 3.3-3.5 (m, 3H), 3.6-3.7 (m, 1H), 4.5-4.8 (m, 1H), 7.1-7.2 (m, 1H), 7.35-7.45 (m, 2H) ppm.
4 ³		496 (m) ⁺	¹ H-NMR (CDCl ₃): δ = 0.05-0.2 (m, 2H), 0.4-0.55 (m, 2H), 0.6-0.8 (m, 1H), 1.2-2.3 (m, 15H), 2.3-2.5 (m, 3H), 2.6-2.8 (m, 2H), 2.8-2.95 (m, 1H), 3.2-3.5 (m, 4H), 3.5-3.7 (m, 2H), 4.55-4.8 (m, 1H), 7.0-7.1 (m, 1H), 7.2-7.45 (m, 2H) ppm.

Footnotes

1. The chromatography eluant was ethyl acetate:methanol:concentrated aqueous ammonia solution (78.4:20:1.6, by volume).
2. The chromatography eluant was dichloromethane:methanol (19:1 changing to 9:1, by volume).
3. The chromatography eluant was dichloromethane:methanol (25:2, by volume).

EXAMPLE 5

5(S)-5-(3,4-Dichlorophenyl)-1-(4,4-difluorocyclohexylmethyl)-5-(2-[3-(4-fluoropiperidin-1-yl)azetidin-1-yl]ethyl)piperidin-2-one



5

To a slurry of the azetidine (see Preparation 13) (241g) in tetrahydrofuran (1700 ml) was added triethylamine (118 ml) and the mixture stirred for 1 hour. A solution of the aldehyde (see Preparations 1 and 15) (294.1g) in THF (800 ml) was then added and the mixture stirred for 3 hours before adding sodium triacetoxyborohydride (194g) and glacial acetic acid (40.3 ml).

10

The slurry was stirred for 2 hours, water (1700 ml) added and the mixture combined with the reaction product from an identical experiment starting from 294g of the aldehyde and 241g of the azetidine.

15

The pH of the mixture was adjusted to 9 with saturated aqueous sodium bicarbonate solution and then it was extracted with ethyl acetate (3 x 2000 ml).

The combined organic layers were concentrated under reduced pressure to provide the impure title compound as a yellow foam (808g).

HPLC analysis showed this to contain 92.4% (by weight) of the title compound.

5

EXAMPLE 6

5(S)-5-(3,4-Dichlorophenyl)-1-(4,4-difluorocyclohexylmethyl)-5-(2-[3-(4-fluoropiperidin-1-yl)]azetidin-1-yl)ethylpiperidin-2-one disuccinate

10 A solution of the compound of Example 5 (752.5g) in acetone (1500 ml) was filtered and further acetone (1500 ml) added to the filtrate. Succinic acid (279g) was added and the solution stirred at room temperature for 1 hour, then at 0°C for 1 hour. The resulting solid was filtered off, washed with acetone and dried to provide the title compound as a white powder (919.5g).

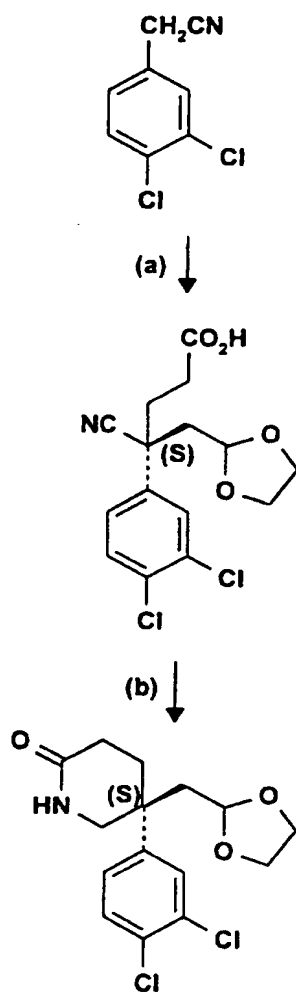
15

The following Preparations illustrate the synthesis of certain intermediates used in the preparation of the compounds of the preceding Examples:-

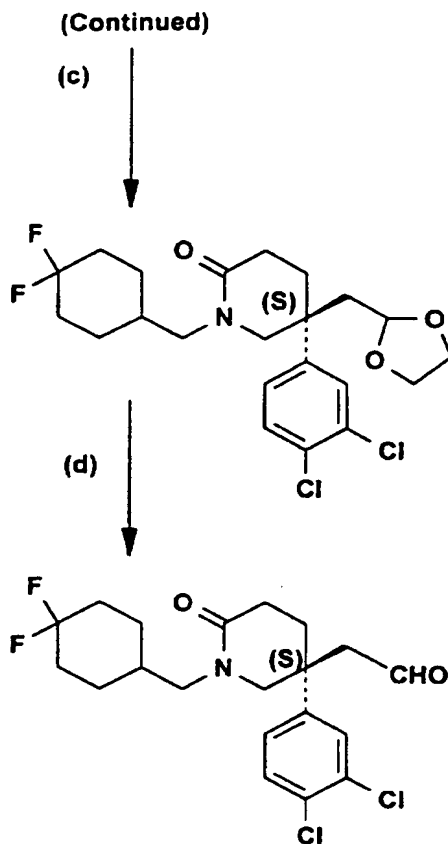
5

PREPARATION 1

5(S)-5-(3,4-Dichlorophenyl)-1-(4,4-difluorocyclohexylmethyl)-5-formylmethylpiperidin-2-one



36



(a) 4(S)-4-Cyano-4-(3,4-dichlorophenyl)-5-(1,3-dioxolan-2-yl)pentan-1-oic acid

- 5 To a 1.0M solution of lithium hexamethyldisilylazide in tetrahydrofuran (4.69l) at 5°C under nitrogen was added a solution of 3,4-dichlorophenylacetonitrile (750 g, 4.28 moles) in tetrahydrofuran (750 ml), dropwise, over 45 minutes. The reaction was allowed to stir for 2 hours. The reaction was cooled again to 5°C and a solution of 2-bromomethyl-1,3-dioxolane (782 g) in tetrahydrofuran (780 ml) added, dropwise, over fifty
- 10 minutes. Tetra-n-butylammonium iodide (75 g) was added, portionwise, and the mixture allowed to warm to room temperature and stirred for 14 hours. The reaction was then cooled to 5°C and 1.0M solution of lithium hexamethyldisilylazide in tetrahydrofuran (4.69l) was added, dropwise. The
- 15 mixture was stirred for 5 hours at room temperature. The solution was cooled to 5°C and a solution of ethyl 3-bromopropanoate (840.5 g) in tetrahydrofuran (840 ml) was added, dropwise, over 50 minutes. The

reaction was allowed to stir for 14 hours. The reaction mixture was cooled to 5°C and 1.5M aqueous sodium hydroxide solution (containing 255 g of sodium hydroxide) was added and the mixture stirred for 14 hours. Water (5l) was added and the mixture was extracted with ethyl acetate (2 x 3l). The combined organic extracts were washed with water (2 x 5l). The aqueous phases were combined and acidified to pH1 using 5N aqueous hydrochloric acid solution and then extracted with ethyl acetate (2 x 3l). The combined organic extracts were concentrated under reduced pressure to a concentration of approximately 3 ml/g based on the theoretical yield of the product.

The above experimental procedure was then repeated on an identical scale.

To the combined organic solutions from both reactions was added (S)-(-)-alpha-methylbenzylamine (1.13 kg) and the mixture stirred for 14 hours. The thick slurry was then stirred with cooling in an ice-bath for 2 hours, filtered, the solid washed with ethyl acetate (2 x 1l) and then dried under reduced pressure at 35°C to give 1.85 kg of material.

A portion of this material (1.34 kg) was dissolved in a mixture of butanone (2l) and water (503 ml) that was heated under reflux. A further portion of butanone (4.7l) was added and the solution was allowed to cool slowly to room temperature overnight. The resulting solid was filtered off, washed with butanone (2 x 1l) and dried under reduced pressure at 35°C for 10 hours to give 563 g of material (93.8% e.e.). A further recrystallisation from butanone/water gave the title compound as a (S)-(-)-alpha-methylbenzylamine salt in 99.8% e.e. To a stirred solution of this salt in ethyl acetate and water was added 5N aqueous hydrochloric acid solution until pH1 was achieved. The mixture was stirred for a further 30 minutes, the layers separated and the aqueous phase extracted with ethyl acetate. The combined organic layers were washed with water and the solvent removed by evaporation under reduced pressure to give the title compound.

¹H-NMR (CDCl₃): δ = 2.05-2.35 (m,4H), 2.4-2.65 (m,2H), 3.7-4.0 (m,4H), 4.75-4.85(m,1H), 7.25-7.55 (m,3H), 9.9 (s.br., 1H, acid) ppm.

5 (b) 5(S)-5-(3,4-Dichlorophenyl)-5-(1,3-dioxolan-2-ylmethyl)piperidin-2(1H)-one

To a solution of the compound of Preparation 1(a) (13.5 g, 39.22 mmol) in glacial acetic acid (130 ml) was added platinum oxide (1.21 g) and the mixture stirred under an atmosphere of hydrogen at 414 kPa (60 psi) and at room temperature for 17 hours. The catalyst was removed by filtration and
10 a further portion of platinum oxide (1.21 g) added. The reaction mixture was then stirred under an atmosphere of hydrogen at 414 kPa (60 psi) and at room temperature for 48 hours. The catalyst was removed by filtration and the solution concentrated under reduced pressure. The residue was dissolved in ethyl acetate (80 ml) and washed with saturated aqueous
15 sodium bicarbonate solution (2 x 75 ml). The organic phase was then separated and the solvent removed under reduced pressure. The resulting solid was stirred in a solution of hexane (20 ml) and ethyl acetate (20 ml) for 2 hours at 0°C and then filtered off to give the title compound (8.15 g).
¹H-NMR (CDCl₃): δ = 1.85-1.95 (m,1H), 2.0-2.25 (m,4H), 2.35-2.4 (m,1H),
20 3.45-3.55 (m,1H), 3.65-3.75 (m,2H), 3.8-3.9 (m,3H), 4.35-4.4 (m,1H), 6.15 (s.br.,1H), 7.2-7.45 (m,3H) ppm.

(c) 5(S)-5-(3,4-Dichlorophenyl)-1-(4,4-difluorocyclohexylmethyl)-5-(1,3-dioxolan-2-ylmethyl)piperidin-2-one

25 To a stirred mixture of dimethyl sulfoxide (10 ml) and potassium hydroxide (340 mg, 4 mol. equiv.) at room temperature under nitrogen was added a solution of the compound of Preparation 1(b) (500 mg, 1.51 mmol) in dimethyl sulfoxide (5 ml). A solution of the compound of Preparation 9
30 (381 mg, 1.1 mol. equiv.) in dimethyl sulfoxide (5 ml) was then added and the mixture stirred at room temperature for 16 hours.

This mixture was then combined with that prepared by a similar method to that described above using the compound of Preparation 1(b) (960 mg, 2.9 mmol) and appropriate amounts of the other reagents.

5

Ethyl acetate (150 ml) was added and the mixture washed with water (3 x 30 ml) followed by brine (1 x 30 ml). The organic layer was dried over anhydrous magnesium sulphate, filtered and evaporated to dryness under reduced pressure. The residue was chromatographed using silica gel eluting with n-pentane: ethyl acetate (1:1 changing to 0:1, by volume) to provide the title compound as a white foam (1.07 g). LRMS $m/z = 462$ (m^+). $^1\text{H-NMR}$ (CDCl_3): $\delta = 1.3\text{--}1.45$ (m, 2H), $1.6\text{--}1.95$ (m, 6H), $2.1\text{--}2.2$ (m, 6H), $2.4\text{--}2.55$ (m, 1H), $3.2\text{--}3.3$ (m, 1H), $3.4\text{--}3.5$ (m, 2H), $3.65\text{--}3.75$ (m, 3H), $3.85\text{--}3.95$ (m, 2H), $4.3\text{--}4.35$ (m, 1H), $7.1\text{--}7.4$ (m, 3H) ppm.

15

(d) 5(S)-5-(3,4-Dichlorophenyl)-1-(4,4-difluorocyclohexylmethyl)-5-formylmethylpiperidin-2-one

A solution of the compound of Preparation 1(c) (3.3 g, 7.14 mmol) in tetrahydrofuran (36 ml) and 5N aqueous hydrochloric acid solution (36 ml) was stirred at room temperature under nitrogen for 90 minutes and then heated at 45°C for a further 90 minutes. The reaction mixture was poured into a mixture of ethyl acetate (40 ml) and saturated aqueous sodium bicarbonate solution (40 ml). The organic phase was separated and the aqueous phase extracted with ethyl acetate (2 x 30 ml). The organic phases were then combined, dried using sodium sulphate, filtered and the solvent removed from the filtrate by evaporation under reduced pressure to give the title compound (2.97 g) which was used without further purification. TLC $R_f = 0.3$ (silica, ethyl acetate). LRMS 418 (m^+).

25

See Preparation 15 for an alternative preparation of this compound.

PREPARATION 25(S)-1-(2-Cyclopropylethyl)-5-(3,4-dichlorophenyl)-5-formylmethylpiperidin-2-one(a) 5(S)-1-(2-Cyclopropylethyl)-5-(3,4-dichlorophenyl)-5-(1,3-dioxolan-2-ylmethyl)piperidin-2-one

The title compound was prepared by a similar method to that of Preparation 1(c) using the compound of Preparation 1(b) and the compound of Preparation 10 as the starting materials. LRMS $m/z = 398 (m+1)^+$.

$^1\text{H-NMR}$ (CDCl_3): $\delta = 0.1\text{-}0.15$ (m, 2H), $0.45\text{-}0.5$ (m, 2H), $0.6\text{-}0.75$ (m, 1H), $1.5\text{-}1.6$ (m, 2H), $1.9\text{-}1.95$ (m, 1H), $2.1\text{-}2.2$ (m, 4H), $2.35\text{-}2.5$ (m, 1H), $3.3\text{-}3.4$ (m, 1H), $3.5\text{-}3.6$ (m, 1H), $3.65\text{-}3.75$ (m, 4H), $3.85\text{-}3.9$ (m, 2H), $4.35\text{-}4.4$ (m, 1H), $7.1\text{-}7.45$ (m, 3H) ppm.

(b) 5(S)-1-(2-Cyclopropylethyl)-5-(3,4-dichlorophenyl)-5-formylmethylpiperidin-2-one

The title compound was prepared by a similar method to that of Preparation 1(d) using the compound of Preparation 2(a) as the starting material. The product obtained was shown to be contaminated with approximately 35 mol % of the dioxolane starting material by $^1\text{H-NMR}$ spectroscopy.

LRMS $m/z = 354 (m+1)^+$.

PREPARATION 33-(4-Fluoropiperidin-1-yl)azetidine dihydrochloride(a) 1-Diphenylmethylazetidin-3-ol

A solution of benzhydrylamine (200 ml, 1.16 mol) and epichlorohydrin (186 ml, 1 mol. equiv.) in methanol (600 ml) was stirred at room temperature for

five days and then heated at 40°C for two days. The solvent was removed under reduced pressure, the residue dissolved in isopropyl alcohol (500 ml) and the solution heated under reflux for six hours. The solution was cooled to room temperature and the precipitate filtered off. This solid was partitioned between dichloromethane (400 ml) and saturated aqueous sodium bicarbonate solution (500 ml). The aqueous phase was extracted with dichloromethane (2 x 400 ml) and the combined organic phases dried over magnesium sulphate. The solution was then filtered and the solvent removed from the filtrate by evaporation under reduced pressure to give the title compound (86 g) as a crystalline solid.

¹H-NMR (CDCl₃): δ = 1.8-2.3 (s,br,1H), 2.85-2.9 (m,2H), 3.5-3.55 (m,2H), 4.35 (s,1H), 4.4-4.5 (m,1H), 7.15-7.4 (m,10H) ppm.

(b) 1-Diphenylmethyl-3-methanesulphonyloxazetidine

To a solution of 1-diphenylmethyloxazetidin-3-ol (see Preparation 3(a)) (65.9 g, 275.7 mmol) in dry dichloromethane (700 ml) at 0°C under nitrogen was added triethylamine (57 ml, 1.5 mol. equiv.). After five minutes, methanesulphonyl chloride (25.6 ml, 1.2 mol. equiv.) was added and the mixture stirred for one hour. Water (300 ml) was then added and the mixture extracted with dichloromethane (3 x 300 ml). The combined organic layers were dried over magnesium sulphate. The solution was then filtered and the solvent removed from the filtrate by evaporation under reduced pressure. The residue was chromatographed using silica gel eluting with methanol:dichloromethane (1:49, by volume) to give the title compound (73.4 g) as a solid.

¹H-NMR (CDCl₃): δ = 2.95 (s,3H), 3.15-3.25 (m,2H), 3.6-3.65 (m,2H), 4.4 (s,1H), 5.05-5.15 (m,1H), 7.15-7.4 (m,10H) ppm.

(c) 1-Diphenylmethyl-3-(4-hydroxypiperidin-1-yl)azetidine

A solution of 1-diphenylmethyl-3-methanesulphonyoxyazetidine (see Preparation 3(b)) (317 g, 1 mol), diethylisopropylamine (155.1 g, 1.2 mol. equiv.) and 4-hydroxypiperidine (121.2 g, 1.2 mol. equiv.) in acetonitrile (500 ml) was heated under reflux for five hours. The solution was cooled to room temperature and the mixture concentrated under reduced pressure. The residue was partitioned between dichloromethane (1.5 l) and saturated sodium bicarbonate solution (500 ml) and the organic phase separated and washed again with saturated sodium bicarbonate solution (2 x 500 ml). The organic phase was then washed with 1M aqueous citric acid solution (2 x 500 ml). The acidic aqueous layer was basified to pH 8.5 using 2N aqueous sodium hydroxide solution (600 ml) at 0°C and then extracted using dichloromethane (1l). The combined organic layers were dried over magnesium sulphate, filtered and evaporated under reduced pressure to give the title compound as a gum (309 g). TLC R_f = 0.2 (silica, methanol:dichloromethane, 1:19, by volume). LRMS m/z = 323 (m+1)⁺. ¹H-NMR (CDCl₃): δ = 1.4-1.6 (m,4H), 1.8-2.0 (m,4H), 2.5-2.65 (m,2H), 2.8-3.0 (m,2H), 3.3-3.4 (m,2H), 3.6-3.8 (m,1H), 4.4 (s,1H), 7.1-7.4 (m,10H) ppm.

The above product can be further purified by conversion to a tosylate salt using para-toluenesulphonic acid and acetone as the solvent, the salt being re-converted to the free base before its use in the next step.

(d) 1-Diphenylmethyl-3-(4-fluoropiperidin-1-yl)azetidine

To a solution of diethylaminosulphur trifluoride (170 g, 1.06 mol) at -60°C in dichloromethane (927 ml) under nitrogen was added a solution of the compound of Preparation 3(c) in dichloromethane (927 ml). The mixture was allowed to warm to room temperature over 2 hours and stirred at room temperature for a further 9 hours. The reaction was then carefully added, dropwise, to aqueous saturated sodium bicarbonate solution (3 l) (an

exotherm resulted). The aqueous layer was separated and the organic layer washed with water (2 x 500 ml). The solvent was removed from the organic layer by evaporation under reduced pressure and the resulting oil purified by chromatography on silica gel eluting with a solvent gradient of dichloromethane changing to dichloromethane:methanol (19.1, by volume) to yield the title compound (172 g). TLC R_f = 0.7 (silica, methanol:dichloromethane, 1.19, by volume).

¹H-NMR (CDCl₃): δ = 1.75-2.0 (m,4H), 2.1-2.3 (m,2H), 2.3-2.5 (m,2H), 2.8-3.05 (m,3H), 3.3-3.4 (m,2H), 4.4 (s,1H), 4.5-4.8 (m,1H), 7.1-7.45 (m,10H) ppm.

The above method can be modified by omitting the chromatography step and instead converting the reaction product to a tosylate salt by treatment with para-toluenesulphonic acid using ethyl acetate as the solvent. The tosylate salt obtained may be used directly in the next step.

(e) 3-(4-Fluoropiperidin-1-yl)azetidine dihydrochloride

To a solution of the compound of Preparation 3(d) (170 g) in dry dichloromethane (1l) at 0°C under nitrogen was added α-chloroethyl chloroformate (149.6 g, 2 mol. equiv.) and the reaction stirred for 1.5 hours. Methanol (10 ml) was then added and the mixture heated under reflux for 15 minutes. The solvent was then removed by evaporation under reduced pressure and the resultant gum triturated with acetone (3 x 300 ml). Hot isopropyl alcohol (500 ml) was then added and the mixture heated at 80°C for 15 minutes. A portion of isopropyl alcohol (150 ml) was then removed by evaporation under reduced pressure and the mixture stirred at 10°C for 0.5 hour. The resultant solid was filtered off and washed with cold isopropyl alcohol (30 ml). This solid was triturated with acetone (600 ml), filtered and dried at 70°C for 4 hours to provide the title compound (69.4 g).

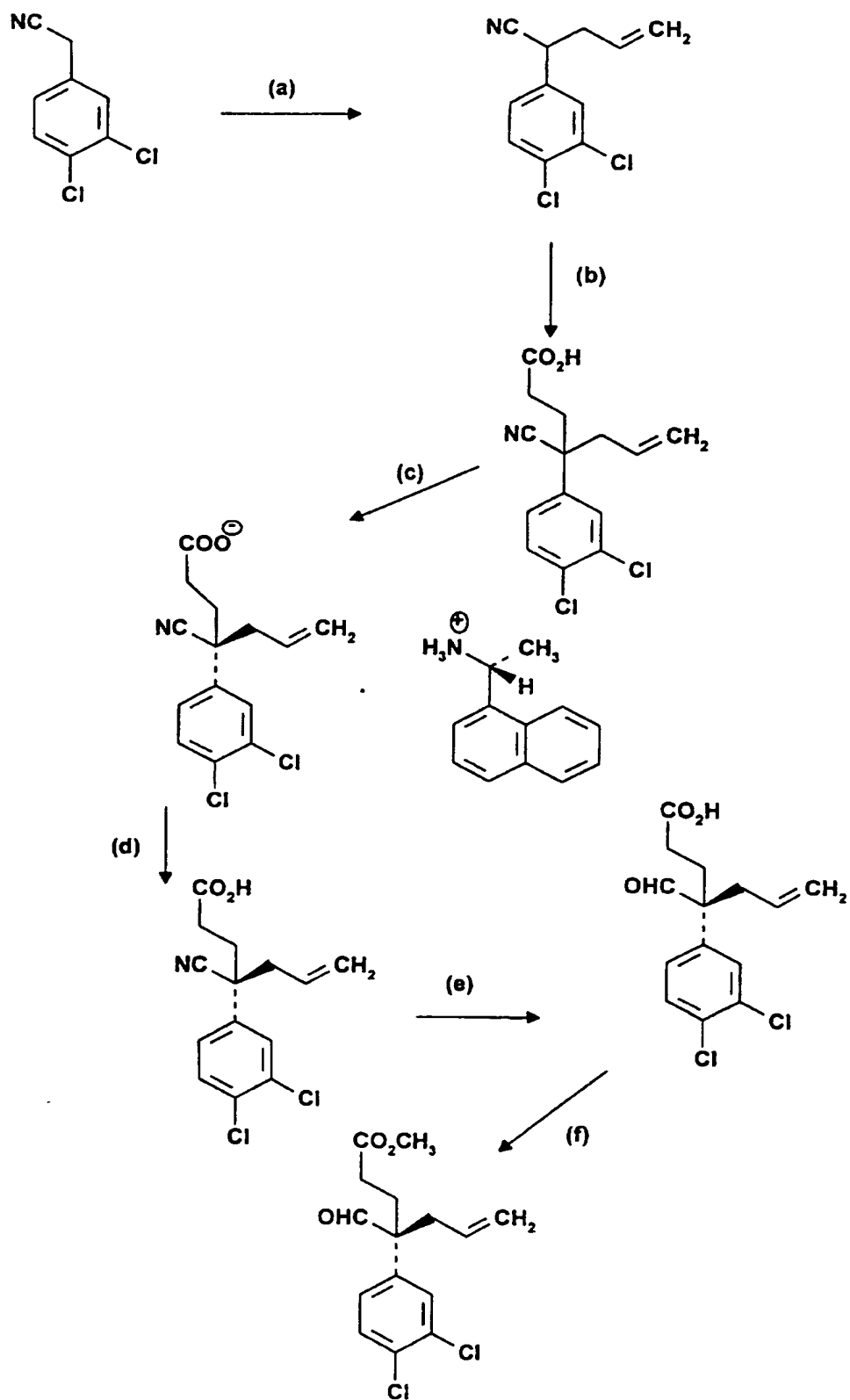
$^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$): δ = 1.9-2.3 (m, 4H), 2.8-4.6 (m, 9H), 4.7-5.2 (m, 1H), 9.1 (s, br., 1H), 9.8 (s, br., 1H), 12.6 (s, br. 1H) ppm.

- 5 See Preparation 13 for the preparation of the corresponding tosylate salt by transfer hydrogenation using the tosylate obtained by the modified method of Preparation 3(d) as the starting material.

PREPARATION 4

- 10 Methyl 4(S)-4-(3,4-dichlorophenyl)-4-formylhept-6-enoate

45



(a) 2-(3,4-Dichlorophenyl)pent-4-enenitrile

To a stirred solution of 3,4-dichlorophenylacetonitrile (800 g, 4.3 mol) in
5 cyclohexane (16 l) at room temperature was carefully added aqueous
sodium hydroxide solution (containing 1600 g of sodium hydroxide in 8l of
water). This addition caused an elevation of the reaction temperature to
50°C. Allyl bromide (572 g, 1.1 mol. equiv.) and tetra-n-butylammonium
10 chloride hydrate (40 g, 0.03 mol. equiv.) were then added and the reaction
stirred for one hour at 50°C. The aqueous phase was removed and the
organic layer washed with water (10l). The organic phase was filtered
through silica gel (1 kg) under reduced pressure to give a yellow filtrate
solution. The solvent was removed from the filtrate under reduced pressure
to give the title compound as an oil (960 g) of 70% purity which was used
15 without any further purification. TLC R_f = 0.71 (silica, diethyl ether:hexane,
1:1, by volume). LRMS m/z = 226 (m)⁺.
¹H-NMR (CDCl₃): δ = 2.6-2.75 (m,2H), 3.85 (t,1H), 5.1-5.25 (m,2H), 5.7-5.9
(m,1H), 7.2-7.25 (m,1H), 7.5-7.55 (m,2H) ppm.

20 (b) 4-Cyano-4-(3,4-dichlorophenyl)hept-6-enoic acid

To a stirred suspension of 60% w/w sodium hydride/oil dispersion (231 g) in
tetrahydrofuran (17l) under nitrogen at -10°C was added a solution of 3-
bromopropanoic acid (806.5 g) in tetrahydrofuran (6l), dropwise over three
25 hours. The reaction was allowed to warm to room temperature over 22
hours. The reaction was then cooled to -10°C.
Simultaneously, a solution of the compound of Preparation 4(a) (1633.5 g)
in tetrahydrofuran (2.5l) was added, dropwise over two hours, to a stirred
suspension of 60% w/w sodium hydride/oil dispersion (221 g) in
30 tetrahydrofuran (2.5l) under nitrogen at -10°C. When the addition was
complete, this mixture was allowed to warm to room temperature over
eighteen hours. This mixture was then cooled to -10°C and cannulated into

the above 3-bromopropanoic acid sodium salt mixture over three hours.

The reaction mixture was heated at 50°C for five hours. The reaction was then cooled, poured into water (8l) and basified to pH 9.3 using aqueous sodium bicarbonate solution. This mixture was washed with

dichloromethane (5 x 2l) and the aqueous portion acidified to pH 1.0 using concentrated hydrochloric acid solution. The aqueous solution was

extracted with dichloromethane (4 x 2.5l) and the organic layers were

combined, dried using anhydrous magnesium sulphate, filtered and the

filtrate concentrated under reduced pressure to give a yellow oil. This oil

was then triturated with hexane (1.5l) to give the title compound as a cream solid (1155.3 g) which was used directly without any further purification.

TLC R_f = 0.42 (silica, methanol:dichloromethane, 1:9, by volume). LRMS m/z = 316 (m+NH₄)⁺.

¹H-NMR (CDCl₃): δ = 2.15-2.8 (m,6H), 5.1-5.25 (m,2H), 5.55-5.7 (m,1H), 7.2-7.25 (m,1H), 7.5-7.55 (m,2H) ppm.

(c) 4(S)-4-Cyano-4-(3,4-dichlorophenyl)hept-6-enoic acid (R)-(+)-1-(1-naphthyl)ethylamine salt

To a solution of the compound of Preparation 4(b) (16 g) in ethyl acetate (50 ml) was added R-(+)-1-(1-naphthyl)ethylamine (4.8 g). The solution was stirred for thirty minutes at room temperature and then the solvent removed under reduced pressure to give a gum. This gum was partially

dissolved in hexane:diethyl ether (4:1, by volume, 150 ml) and the sides of the flask scratched to induce crystallisation. The white solid that formed was filtered off and crystallised three times from ethyl acetate to give the title compound (4.9 g). m.p. 153-154°C.

[α]_D²⁵ -7.1° (c = 0.0012).

¹H-NMR (CDCl₃): δ = 1.6 (d,3H), 2.0-2.2 (m,2H), 2.25-2.5 (m,2H), 2.5-2.7 (m,2H), 3.8-4.1 (s,br,3H), 5.0-5.2 (m,3H), 5.5-5.7 (m,1H), 7.15-7.25 (m,1H),

7.4-7.6 (m,6H), 7.75 (d,1H), 7.9 (d,1H), 8.1 (d,1H) ppm.

(d) 4(S)-4-Cyano-4-(3,4-dichlorophenyl)hept-6-enoic acid

5

To a stirred solution of the compound of Preparation 4(c) (5.5 g) in dichloromethane (100 ml) was added 1N aqueous hydrochloric acid solution (100 ml). The aqueous layer was then removed and the organic portion washed with 1N aqueous hydrochloric acid solution (70 ml). The organic layer was dried using anhydrous magnesium sulphate, filtered and the filtrate evaporated to dryness under reduced pressure to give the title compound (3.6 g). LRMS $m/z = 316 (m+NH_4)^+$. 1H -NMR ($CDCl_3$): $\delta = 2.15$ - 2.8 (m,6H), 5.1 - 5.25 (m,2H), 5.55 - 5.7 (m,1H), 7.2 - 7.25 (m,1H), 7.5 - 7.55 (m,2H) ppm.

15

(e) 4(S)-4-(3,4-Dichlorophenyl)-4-formylhept-6-enoic acid

To a solution of the compound of Preparation 4(d) (2 g, 6.7 mmol) in toluene (20 ml) at $-78^\circ C$ under an atmosphere of dry nitrogen was added, dropwise, diisobutylaluminium hydride (8.9 ml of a 1.5 M solution in toluene, 2 mol. equiv.). The mixture was then allowed to warm to $-40^\circ C$ over three hours. The reaction was cooled to $-78^\circ C$ and diisobutylaluminium hydride (3 ml of a 1.5 M solution in toluene, 0.66 mol. equiv.) added, dropwise. After one hour a further addition of diisobutylaluminium hydride (1.5 ml of a 1.5 M solution in toluene, 0.33 mol. equiv.) was made and the mixture stirred at $-78^\circ C$ for one hour.

The reaction mixture was carefully poured into stirred 10% w/w aqueous citric acid solution (60 ml). The mixture was stirred rapidly for 30 minutes. The organic layer was then separated, dried using magnesium sulphate, filtered and the filtrate evaporated to dryness under reduced pressure to provide the title compound which was used directly without further purification.

30

¹H-NMR (CDCl₃): δ = 2.0-2.5 (m,4H), 2.5-2.9 (m,2H), 5.0-5.3 (m,2H), 5.5-5.7 (m,1H), 7.0-7.5 (m,3H), 4.5 (s,br, 1H) ppm.

5 (f) Methyl 4(S)-4-(3,4-dichlorophenyl)-4-formylhept-6-enoate

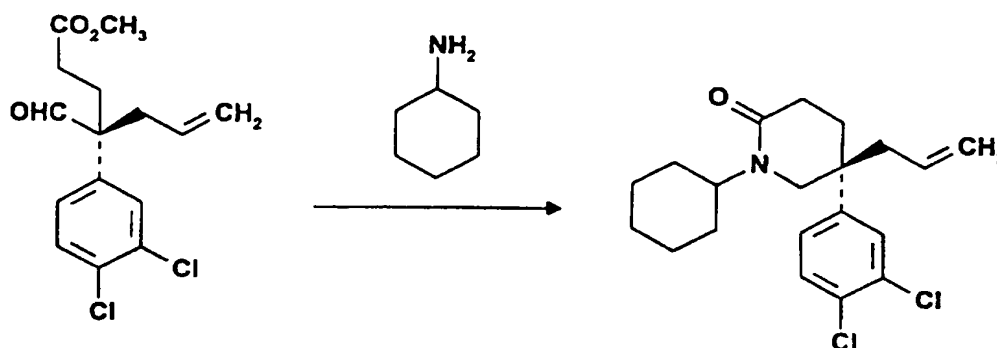
To a solution of the compound of Preparation 4(e) (1.34 g, 4.45 mmol) in dichloromethane (50 ml) under nitrogen at room temperature was added 1-hydroxybenzotriazole hydrate (0.63 g, 1 mol. equiv.) and 1-(3-
10 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.19 g, 1.4 mol. equiv.). The mixture was stirred for 10 minutes then methanol (0.9 ml, 5 mol. equiv.) was added. The reaction mixture was then stirred at room temperature for three hours.

The solvent was removed by evaporation under reduced pressure and the
15 residue partitioned between ethyl acetate (50 ml) and 0.5 N aqueous hydrochloric acid solution (20 ml). The organic layer was separated, dried using sodium sulphate, filtered and the filtrate evaporated to dryness under reduced pressure to provide the title compound (1.6 g) which was used directly without further purification.

20 ¹H-NMR (CDCl₃): δ = 2.0-3.0 (m,6H), 3.6 (s,3H), 4.9-5.7 (m,3H), 7.0-7.1 (m,1H), 7.2-7.8 (m,2H), 9.5 (s,1H) ppm.

PREPARATION 55(S)-5-Allyl-1-cyclohexyl-5-(3,4-dichlorophenyl)piperidin-2-one

5

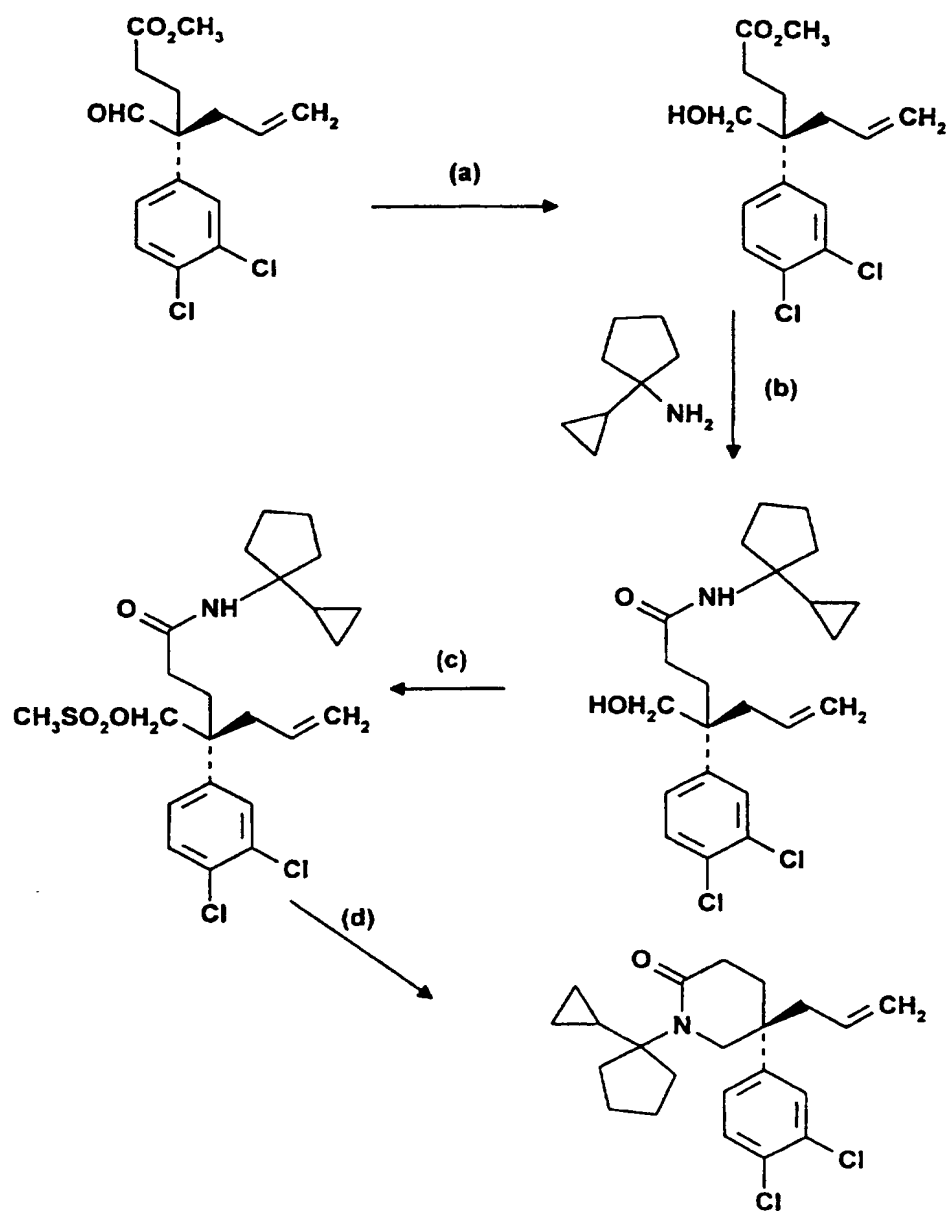


To a solution of the compound of Preparation 4(f) (500 mg, 1.6 mmol) and cyclohexylamine (200 μ l, 1.1 mol. equiv.) in tetrahydrofuran (30 ml) at room temperature under nitrogen was added sodium triacetoxyborohydride (470 mg, 1.4 mol. equiv.) and acetic acid (91 μ l, 1 mol. equiv.). The reaction was stirred for 18 hours at room temperature and then heated under reflux for four hours. The mixture was then cooled and poured into saturated aqueous sodium carbonate solution (20 ml). The mixture was extracted with ethyl acetate (3 x 50 ml). The combined organic layers were then dried using sodium sulphate, filtered and the filtrate evaporated to dryness under reduced pressure. The residue was chromatographed using silica gel eluting with methanol:dichloromethane (1:49, by volume). The material obtained by chromatography was taken up in tetrahydrofuran (50 ml) and the solution heated under reflux for 14 hours. The solvent was removed by evaporation under reduced pressure and the residue chromatographed using silica gel eluting with methanol:dichloromethane (1:9, by volume). The material obtained was then rechromatographed using silica gel eluting with a solvent gradient of dichloromethane:hexane:methanol (9:1:0 changing to 199:0:1, by volume) to provide the title compound as an oil (281 mg). TLC Rf = 0.2 (methanol:dichloromethane, 2:98, by volume). LRMS m/z = 366 (m)⁺.

51

$^1\text{H-NMR}$ (CDCl_3): δ = 1.0-1.2 (m, 1H), 1.4-2.5 (m, 15H), 3.2-3.3 (m, 1H), 3.4-3.5 (m, 1H), 4.4-4.6 (m, 1H), 5.0-5.2 (m, 2H), 5.3-5.5 (m, 1H), 7.0-7.1 (m, 1H), 7.3-7.5 (m, 2H) ppm.

5

PREPARATION 65(S)-5-Allyl-1-(1-cyclopropylcyclopent-1-yl)-5-(3,4-dichlorophenyl)piperidin-2-one

(a) Methyl 4(S)-4-(3,4-dichlorophenyl)-4-hydroxymethylhept-6-enoate

To a solution of the compound of Preparation 4(f) (1.6 g, 5 mmol) in tetrahydrofuran (45 ml) at room temperature under an atmosphere of nitrogen was added sodium triacetoxymethylborohydride (1.494 g, 1.4 mol. equiv.) and acetic acid (0.29 ml, 1 mol. equiv.). After 5 minutes, triethylamine (1.40 ml, 2 mol. equiv.) was added, and the reaction stirred at room temperature for 18 hours. The solvent was removed by evaporation under reduced pressure and the residue partitioned between saturated aqueous sodium bicarbonate solution (30 ml) and ethyl acetate (30 ml). The organic layer was separated and the aqueous portion extracted with ethyl acetate (2 x 30 ml). The combined organic layers were dried using sodium sulphate and evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate:hexane (1:2, by volume) to give the title compound (307 mg). TLC R_f = 0.34 (silica, ethyl acetate:hexane, 1:2, by volume).

(b) N-(1-Cyclopropylcyclopent-1-yl)-4(S)-4-(3,4-dichlorophenyl)-4-hydroxymethylhept-6-enamide

A mixture of the compound of Preparation 6(a) (0.73 g, 2.3 mmol) and the compound of Preparation 11 (0.32g, 1.1 mol. equiv.) was heated at 100°C in a sealed flask for 16 hours. A further portion of the compound of Preparation 11 (158 mg, 0.55 mol. equiv.) was then added and the mixture again heated in a sealed flask at 100°C for a further 16 hours. The reaction mixture was cooled and partitioned between ethyl acetate (30 ml) and 1N aqueous hydrochloric acid solution (20 ml). The organic layer was separated, dried using sodium sulphate, filtered and the solvent removed from the filtrate by evaporation under reduced pressure. The residue was chromatographed using silica gel eluting with ethyl acetate:hexane (1:1, by volume) to provide the title compound (0.8 g). LRMS m/z = 410 (m)⁺.

¹H-NMR (CDCl₃): δ = 0.2-0.3 (m,2H), 0.3-0.5 (m,2H), 1.2-1.8 (m,10H), 1.8-2.2 (m,5H), 2.3-2.6 (m,2H), 3.6-3.8 (m,2H), 4.9-5.3 (m,2H), 5.4-5.6 (m,1H), 7.1-7.15 (m,1H), 7.3-7.5 (m,2H) ppm.

5

(c) N-(1-Cyclopropylcyclopent-1-yl)-4(S)-4-(3,4-dichlorophenyl)-4-methanesulphonyloxymethylhept-6-enamide

10

To a solution of the compound of Preparation 6(b) (0.77 g, 1.88 mmol) in dichloromethane (20 ml) at 0°C under nitrogen was added triethylamine (0.327 ml, 1.25 mol. equiv.) followed by methanesulphonyl chloride (0.17 ml, 1.2 mol. equiv.). The reaction was stirred for 90 minutes. The solvent was removed by evaporation under reduced pressure and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic layer was separated, dried using sodium sulphate, filtered and the solvent removed from the filtrate by evaporation under reduced pressure. The resulting oil was chromatographed using silica gel eluting with dichloromethane:methanol (19:1, by volume) to provide the title compound (0.88 g).

15

20

¹H-NMR (CDCl₃): δ = 0.2-0.25 (m,2H), 0.3-0.45 (m,2H), 1.2-1.8 (m,8H), 1.8-2.2 (m,6H), 2.4-2.6 (m,2H), 2.95 (s,3H), 4.3-4.4 (m,2H), 5.05-5.3 (m,2H), 5.5-5.65 (m,1H), 7.1-7.2 (m,1H), 7.35-7.5 (m,2H) ppm.

25

(d) 5(S)-5-Allyl-1-(1-cyclopropylcyclopent-1-yl)-5-(3,4-dichlorophenyl)piperidin-2-one

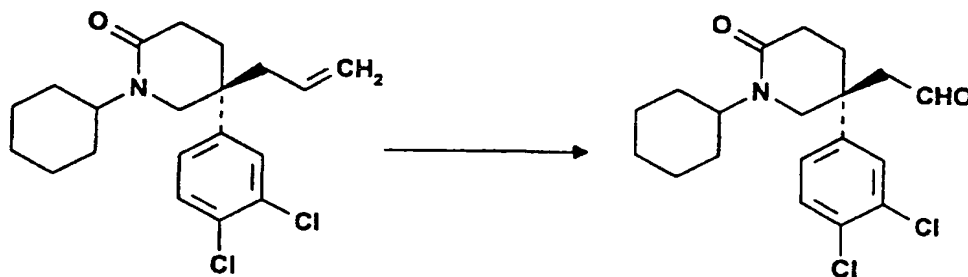
30

To a solution of the compound of Preparation 6(c) (0.88 g, 1.8 mmol) in tetrahydrofuran (10 ml) was added 60% w/w sodium hydride/oil dispersion (108 mg, 1.5 mol. equiv.). The mixture was stirred for 30 minutes at room temperature under an atmosphere of nitrogen. After this period of time the reaction was heated under reflux for 16 hours. The mixture was then partitioned between a 2% w/w aqueous sodium carbonate solution

(40 ml) and ethyl acetate (40 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 30 ml). The combined organic layers were dried using magnesium sulphate, filtered and evaporated to dryness under reduced pressure. The residue was chromatographed using silica gel eluting with dichloromethane:diethyl ether (19:1, by volume) to provide the title compound (0.525 g). TLC R_f = 0.15 (silica, ethyl acetate:hexane, 1:4, by volume). LRMS m/z = 392 (m)⁺. ¹H-NMR (CDCl₃): δ = 0.3-0.5 (m, 4H), 1.4-1.5 (m, 1H), 1.5-1.8 (m, 4H), 1.8-2.3 (m, 7H), 2.3-2.5 (m, 2H), 2.5-2.6 (m, 1H), 3.4-3.45 (m, 1H), 3.6-3.65 (m, 1H), 4.9-5.1 (m, 2H), 5.3-5.5 (m, 1H), 7.15-7.2 (m, 1H), 7.35-7.5 (m, 2H) ppm.

PREPARATION 7

5(S)-1-Cyclohexyl-5-(3,4-dichlorophenyl)-5-formylmethylpiperidin-2-one



Into a solution of the compound of Preparation 5 (0.358 g, 1 mol. equiv.) in methanol (28 ml) under nitrogen at -78°C was bubbled ozone at a rate of 50 ml/min. (using a charge of 1.5A to generate the ozone from oxygen) for 15 minutes. After this time the amperage was reduced to zero and oxygen bubbled through the reaction at a rate of 5 ml/min. for two minutes. The oxygen supply was then removed and nitrogen bubbled through the reaction mixture for twenty minutes. After this time, a solution of dimethyl sulphide (0.72 ml, 10 mol. equiv.) in methanol (2 ml) was cautiously added, dropwise, and the reaction left to warm to

room temperature over eighteen hours. The solvent was removed under reduced pressure and the reaction mixture was partitioned between ethyl acetate (20 ml) and water (15 ml). The organic layer was separated and the aqueous portion further extracted with ethyl acetate (2 x 20 ml). The organic layers were then combined, dried using sodium sulphate, filtered and the filtrate evaporated to dryness under reduced pressure to give the title compound (0.361 g) which was used without further purification. TLC R_f = 0.31 (silica, methanol:dichloromethane, 1:19, by volume).

¹H-NMR (CDCl₃): δ = 0.2-0.4 (m, 2H), 0.5-0.7 (m, 2H), 1.0-1.15 (m, 1H), 2.0-2.25 (m, 2H), 2.3-2.45 (m, 1H), 2.6-2.8 (m, 1H), 2.9-3.05 (m, 1H), 3.1-3.2 (m, 1H), 3.4-3.6 (m, 2H), 3.9-4.0 (m, 1H), 4.05-4.15 (m, 1H), 7.15-7.2 (m, 1H), 7.3-7.5 (m, 2H), 9.5 (s, 1H), ppm.

PREPARATION 8

5(S)-1-(1-Cyclopropylcyclopent-1-yl)-5-(3,4-dichlorophenyl)-5-formylmethylpiperidin-2-one

The title compound was prepared by a similar procedure to that described in Preparation 7 using the compound of Preparation 6(d) as the starting material.

PREPARATION 9

4,4-Difluoro-1-(methanesulphonyloxymethyl)cyclohexane

(a) 4,4-Difluorocyclohexylmethanol

To a solution of diethylaminosulphur trifluoride (200 ml, 2 mol. equiv.) in dichloromethane (1500 ml) at 0°C was added a solution of ethyl 4-oxocyclohexanecarboxylate (130 g) in dichloromethane (500ml), dropwise, over 20 minutes. The mixture was allowed to stir at room temperature overnight. Water (250 ml) was then added carefully (CAUTION: strong

exotherm). The mixture was basified with saturated aqueous sodium bicarbonate solution, extracted with dichloromethane and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulphate, filtered and the solvent removed by evaporation under reduced pressure to give an orange/red oil that was distilled under reduced pressure to provide contaminated ethyl 4,4-difluorocyclohexanecarboxylate as a yellow oil (110.7 g), b.p. 60-70°C at 2 mm Hg.

A portion of this product (1.96 g) was dissolved in dry diethyl ether (15 ml) and added, dropwise, to a stirred suspension of lithium aluminium hydride (350 mg) in dry diethyl ether (30 ml) at 0°C under nitrogen. The mixture was then allowed to stir for one hour. Water (0.5 ml) was then added followed by 2N aqueous sodium hydroxide solution (0.5 ml) and then water (0.5 ml). The inorganic solids were removed by filtration and the filtrate concentrated by evaporation under reduced pressure to give the contaminated title compound as a colourless oil (1.59 g).

This product was purified on a larger scale by dissolving 5 g of this material in acetone (420 ml) and adding sodium bicarbonate (21 g) and water (105 ml). A solution of OXONE (trade mark) (21 g) in water (105 ml) was then added and the mixture stirred for 1.5 hours. The acetone was removed by evaporation under reduced pressure. 10% w/w Aqueous sodium bicarbonate solution (50 ml) was then added and the mixture extracted with dichloromethane (3 x 50 ml). The combined organic extracts were then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide the purified title compound as a colourless oil (2.4 g).

In a modification of the above procedure, ethyl 4,4-difluorocyclohexanecarboxylate may be prepared from ethyl 4-oxocyclohexanecarboxylate using SF₄/HF and dichloromethane as the solvent in an autoclave. With this method, the use of OXONE in the work-up is not necessary.

For an alternative preparation of 4,4-difluorocyclohexylmethanol from ethyl 4,4-difluorocyclohexanecarboxylate see Preparation 12.

5 (b) 4,4-Difluoro-1-(methanesulphonyloxymethyl)cyclohexane

To a solution of the compound of Preparation 9(a) (24.4 g, 162.5 mmol) in dry dichloromethane (800 ml) at 0°C under an atmosphere of nitrogen was slowly added triethylamine (34 ml, 1.5 mol equiv.) and methanesulphonyl chloride (12.6 ml, 1 mol equiv.) The reaction mixture was stirred for 16 hours at room temperature. Dichloromethane (200 ml) was added and the mixture washed successively with saturated aqueous sodium bicarbonate solution (2 x 200 ml), 1N aqueous hydrochloric acid solution (2 x 500 ml) and brine (350 ml). The organic layer was dried over anhydrous sodium sulphate, filtered and evaporated to dryness under reduced pressure to provide a brown oil which crystallised on standing to provide a cream solid (34.7 g). LRMS $m/z = 246 (m+18)^+$.

$^1\text{H-NMR}$ (CDCl_3): $\delta = 1.2\text{--}1.5$ (m, 2H), $1.55\text{--}1.9$ (m, 5H), $2.0\text{--}2.2$ (m, 2H), 3.0 (s, 3H), $4.0\text{--}4.1$ (m, 2H) ppm.

CAUTION

It has been noted that the products of Preparations 9(a) and 9(b) are thermally unstable and display autocatalytic decomposition, the onset temperature for which is lowered in the presence of acid. It is therefore recommended that the use of acid is avoided in the work-up and that only basic conditions are used.

PREPARATION 10

2-Methanesulphonyloxyethylcyclopropane

To a solution of 2-cyclopropylethanol (2.1 g, 24.4 mmol) in dichloromethane (50 ml) at 0°C under nitrogen was added triethylamine (4.1 ml, 1.2 mol. equiv.).

Methanesulphonyl chloride (2.5 ml, 1.3 mol. equiv.) was added, dropwise, and the reaction allowed to stir for 18 hours at room temperature. Water (50 ml) and dichloromethane (50 ml) were added. The organic phase was separated, washed with water (2 x 50 ml) and then dried over anhydrous sodium sulphate. The solution was filtered and the solvent removed from the filtrate by evaporation under reduced pressure to give the title compound as an oil (4 g). TLC R_f = 0.9 (silica, methanol:dichloromethane, 1:19, by volume). LRMS m/z = 182 (m+18)⁺. ¹H-NMR (CDCl₃): δ = 0.1-0.15 (m,2H), 0.5-0.55 (m,2H), 0.7-0.8 (m,1H), 1.6-1.7 (m,2H), 3.00 (s,3H), 4.25-4.3 (m,2H) ppm.

PREPARATION 11

1-Amino-1-cyclopropylcyclopentane

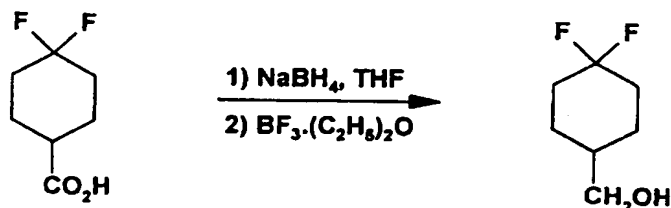
15 (a) 1-Cyclopropylcyclopentan-1-ol

To a solution of bromocyclopropane (2.54 ml, 31.7 mmol) in diethyl ether (50 ml) at -78°C under nitrogen was added, dropwise, tert-butyllithium (18.2 ml of a 1.7 M solution in pentane, 31 mmol). Diethyl ether (30 ml) was then added and the mixture stirred for 1 hour at -78°C. A solution of cyclopentanone (2.74 ml, 34 mmol) in diethyl ether (40 ml) was then added dropwise. The reaction was stirred for 4 hours at -78°C and was then allowed to warm to room temperature over 16 hours. Water (40 ml) was added, cautiously, and the aqueous layer extracted with diethyl ether (2 x 40 ml). The combined ether layers were dried using sodium sulphate, filtered and evaporated under reduced pressure to give an oily residue. This was chromatographed using silica gel eluting with a solvent gradient of dichloromethane:methanol (100:0 changing to 9:1, by volume) to provide the title compound (3.5 g). TLC R_f = 0.4 (silica, dichloromethane:methanol, 9:1, by volume). ¹H-NMR (CDCl₃): δ = 0.3-0.5 (m,4H), 1.05-1.15 (m,2H), 1.5-1.7 (m,6H), 1.7-1.9 (m,2H) ppm.

(b) 1-Amino-1-cyclopropylcyclopentane

To a solution of sodium azide (3.5 g, 54 mmol) in toluene (25 ml) under nitrogen at room temperature was added trifluoroacetic acid (4 ml, 53 mmol). The mixture was cooled to 0°C and a solution of the compound of Preparation 11(a) (3.35 g, 26.5 mmol) in toluene (5 ml) was added, dropwise. The mixture was stirred for 4 hours and allowed to warm to room temperature. Concentrated ammonium hydroxide solution (25 ml) was then added. The toluene layer was separated and washed with water (2 x 20 ml). The organic layer was dried using sodium sulphate and filtered. The filtrate was added, dropwise, to a 1M solution of lithium aluminium hydride in tetrahydrofuran (53 ml) at 5°C under nitrogen. The mixture was stirred at room temperature for sixteen hours and at 50°C for one hour. Water (1.8 ml) was then added, dropwise, followed by 3N aqueous sodium hydroxide solution (1.8 ml) and water (5.4 ml). The mixture was stirred for 20 minutes filtered and evaporated under reduced pressure to a volume of approximately 20 ml. The solution was washed with 10% w/w aqueous sodium bicarbonate solution (30 ml) and dried using sodium sulphate. The solvent was removed by evaporation under reduced pressure to provide the title compound (2 g) which was used directly without further purification.

¹H-NMR (CDCl₃): δ = 0.15-0.4 (m,4H), 0.8-1.2 (m,3H), 1.3-1.9 (m,8H) ppm.

PREPARATION 124,4-Difluorocyclohexylmethanol

To a slurry of sodium borohydride (74.66g) in tetrahydrofuran (1500ml) at 4°C was added a solution of 4,4-difluorocyclohexanecarboxylic acid (322.6g) (prepared by conventional hydrolysis of ethyl 4,4-difluorocyclohexanecarboxylate [see Preparation 9(a)] using sodium hydroxide in aqueous ethanol) in tetrahydrofuran (1000 ml) over a 70 minute period maintaining the reaction temperature below 10°C by external cooling. The slurry was stirred for 1 hour, cooled to 3°C and boron trifluoride etherate (241 ml) added over 40 minutes maintaining the reaction temperature below 15°C. The reaction was then stirred at room temperature for 18 hours.

10

15

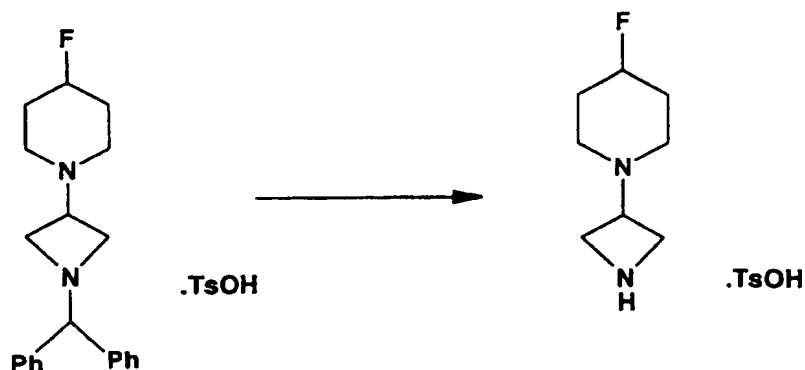
95% Aqueous ethanol (1900 ml) was then added over a 5 minute period and this resulted in an initial exotherm causing the reaction temperature to rise from 19 to 23°C with the rapid evolution of gas. The reaction temperature then dropped to 19°C during the remainder of the addition. The slurry was stirred for 30 minutes and the solvent removed by evaporation under reduced pressure. The residue was dissolved in a 1:1, by volume, dichloromethane:water (2500 ml) and the layers separated. The aqueous layer was further extracted with dichloromethane (600 ml) and the combined organic layers concentrated under reduced pressure to provide the title compound as an orange oil (281.7 g).

20

25

PREPARATION 133-(4-Fluoropiperidin-1-yl)azetidine tosylate

5



(Ts - tosyl)

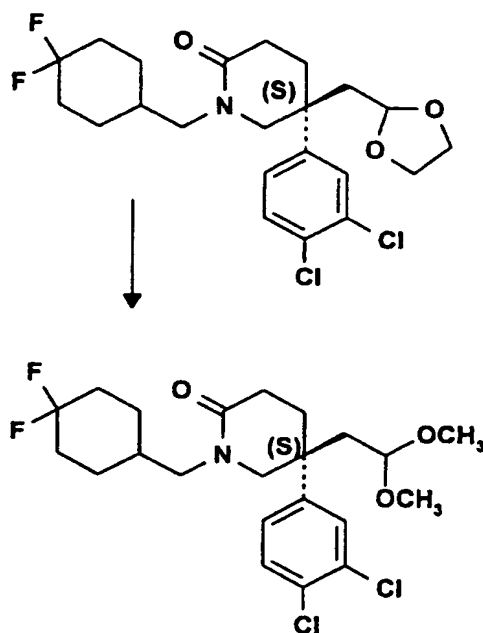
A slurry of 3-(4-fluoropiperidin-1-yl)-1-diphenylmethyldiazetidine tosylate (578 g) (see the modified procedure of Preparation 3(d)) in methanol (8670 ml) was warmed to 45°C to achieve solution. Fuller's earth (trade mark) (231 g) was added and the green slurry stirred for 2.5 hours at about 50°C. The mixture was filtered and the filtrate stirred overnight at room temperature. The yellowish slurry was heated to 55°C, activated carbon (NORIT A, trade mark) (289 g) was added and the mixture heated under reflux for 1 hour. The mixture was cooled and filtered through a filter aid (ARBACEL, trade mark), 10% w/w palladium/carbon (containing 50% by weight of water) (231 g) and ammonium formate (283.4 g) were added to the filtrate and the mixture heated under reflux for 2.5 hours. Further 10% w/w palladium/carbon (containing 50% by weight of water) (115 g) was added and the heating under reflux continued for 1 hour. The reaction mixture was cooled, filtered through a filter aid (ARBACEL, trade mark) and the filtrate concentrated under reduced pressure to give an oily white solid that was allowed to stand for 48 hours. This solid was then granulated in ethyl acetate (3000 ml) for 30 minutes and the resulting white solid filtered off and dried to

provide the title compound as a white solid (282.7 g). ¹H-NMR analysis showed the molar ratio of free base:para-toluenesulphonic acid to be 1:1.15-1.35.

5

PREPARATION 14

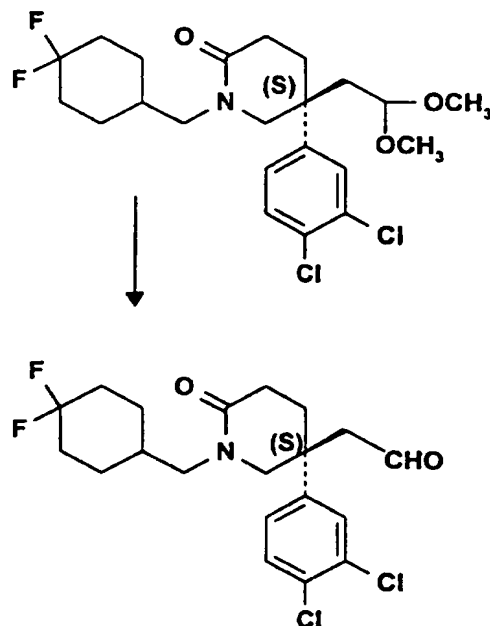
5(S)-5-(3,4-Dichlorophenyl)-1-(4,4-difluorocyclohexylmethyl)-5-(2,2-dimethoxyethyl)piperidin-2-one



10

To a solution of the compound of Preparation 1(c) (238g) in methanol (2400 ml) was added Amberlyst 15 (trade mark) ion exchange resin (120g) and the slurry stirred at room temperature for 24 hours. The mixture was filtered, the filtrate concentrated under reduced pressure and the residual yellow gum taken up in dichloromethane (2000 ml) and washed with water (3 x 2000 ml). The organic layer was concentrated under reduced pressure and the residue taken up in methyl t-butyl ether (500 ml). The mixture was concentrated under reduced pressure to a volume of about 250 ml and the slurry then stirred for 2 hours. The resulting white solid was filtered off and dried to provide the title compound (180.66g).

20

PREPARATION 155(S)-5-(3,4-Dichlorophenyl)-1-(4,4-difluorocyclohexylmethyl)-5-formylmethylpiperidin-2-one

To a stirred solution of the compound of Preparation 14 (179.25g) in tetrahydrofuran (900 ml) was added 1N aqueous hydrochloric acid solution (900 ml). The mixture was stirred at room temperature for 24 hours and then the organic solvent removed under reduced pressure. The aqueous residue was extracted with dichloromethane (3 x 600 ml), the organic layers combined and the solvent removed under reduced pressure to give a white solid (163.8g). This material was slurried in methyl isobutyl ketone (250 ml) for 1 hour. The solid obtained was filtered off and dried to provide the title compound (145.15g).

PHARMACOLOGICAL DATA

The affinity of a selection of the compounds of the preceding Examples for the human NK₂ receptor was tested in vitro by testing their ability to compete with [³H] NKA for binding to membranes prepared from Chinese hamster ovary cells expressing the cloned human NK₂ receptor using the method set out on page 26.

The results obtained are tabulated below.

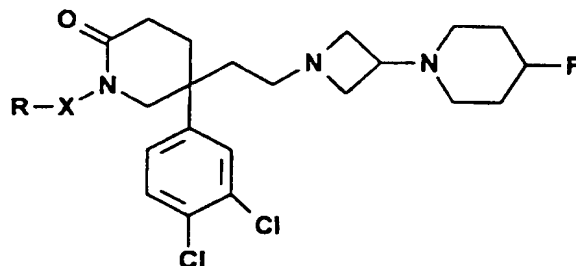
Example no.	pKi
1	9.2
2	10.3
3	10.0
4	8.6

The "pKi" measurement is the negative logarithm of the molar affinity of the compound for the receptor as determined in radioligand binding assays using standard protocols.

65

CLAIMS

1. A compound of the formula:-



(I)

5

or a pharmaceutically acceptable acid addition salt thereof,

wherein X is a direct link or C₁-C₄ alkylene; and

R is C₃-C₇ cycloalkyl optionally substituted by 1 or 2 substituents each

10

independently selected from fluoro and C₃-C₇ cycloalkyl:

with the proviso that X is not methylene when R is cyclopropyl.

2. A compound as claimed in claim 1 wherein X is a direct link, methylene or ethylene.

15

3. A compound as claimed in claim 1 or 2 wherein X is methylene.

4. A compound as claimed in any preceding claim wherein R is C₃-C₆ cycloalkyl optionally substituted by 1 or 2 substituents each independently selected from fluoro and cyclopropyl.

20

5. A compound as claimed in any preceding claim wherein R is cyclopropyl, 1-cyclopropylcyclopent-1-yl, cyclohexyl or 4,4-difluorocyclohexyl.

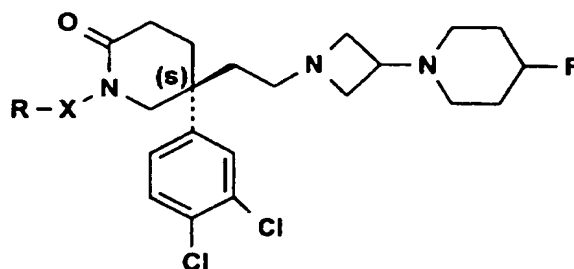
6. A compound as claimed in any preceding claim wherein R is 4,4-difluorocyclohexyl.

25

7. A compound as claimed in claim 1 wherein R-X is 4,4-difluorocyclohexylmethyl, cyclohexyl, 1-cyclopropylcyclopent-1-yl or 2-cyclopropylethyl.

5

8. A compound as claimed in any preceding claim of the formula:



(IA)

wherein X and R are as defined in the respective preceding claim.

10

9. 5(S)-5-(3,4-Dichlorophenyl)-1-(4,4-difluorocyclohexylmethyl)-5-(2-[3-(4-fluoropiperidin-1-yl)]azetidin-1-yl)ethylpiperidin-2-one or an acid addition salt thereof.

15

10. 5(S)-5-(3,4-Dichlorophenyl)-1-(4,4-difluorocyclohexylmethyl)-5-(2-[3-(4-fluoropiperidin-1-yl)]azetidin-1-yl)ethylpiperidin-2-one disuccinate.

20

11. A pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable acid addition salt thereof, as claimed in any preceding claim, together with a pharmaceutically acceptable diluent or carrier.

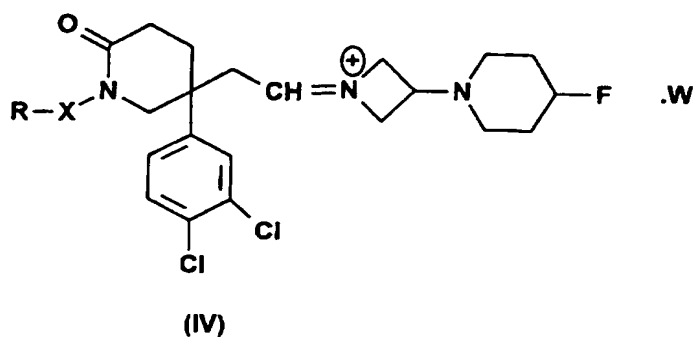
12. A compound of the formula (I), or a pharmaceutically acceptable acid addition salt or composition thereof, as claimed in any of claims 1 to 10 and 11, respectively, for use as a medicament.

25

13. The use of a compound of the formula (I), or of a pharmaceutically acceptable acid addition salt or composition thereof, as claimed in any of claims 1 to 10 and 11, respectively, for the manufacture of a medicament for the treatment of a disease by producing an antagonist effect on a tachykinin acting at the human NK₁, NK₂ or NK₃ receptor, or any combination thereof.
14. Use as claimed in claim 13 where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, an urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain.
15. A method of treatment of a human to treat a disease by producing an antagonist effect on a tachykinin acting at the human NK₁, NK₂ or NK₃ receptor, or any combination thereof, which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable acid addition salt or composition thereof, as claimed in any of claims 1 to 10 and 11, respectively.
16. A method as claimed in claim 15 where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, an urogenital tract disorder such as incontinence, hyperreflexia

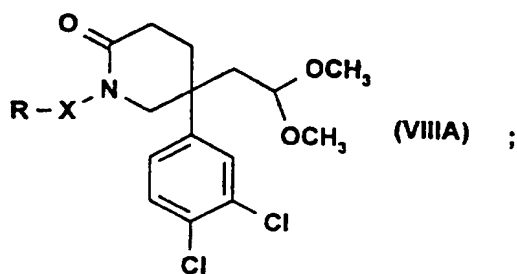
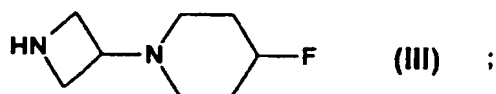
or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain.

17. A compound of the formula:

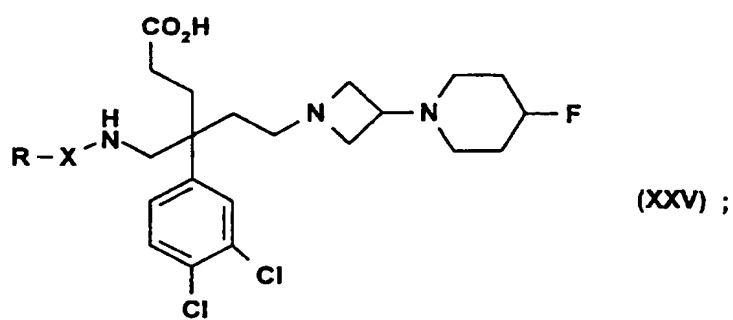
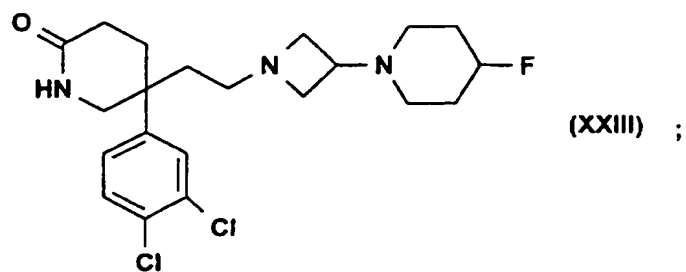


where W is an anion;

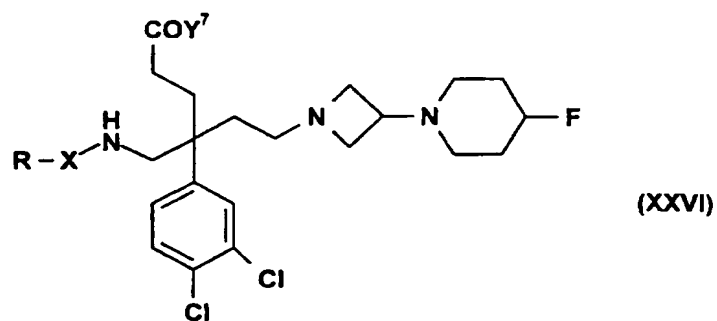
a para-toluenesulphonate salt of a compound of the formula:



69

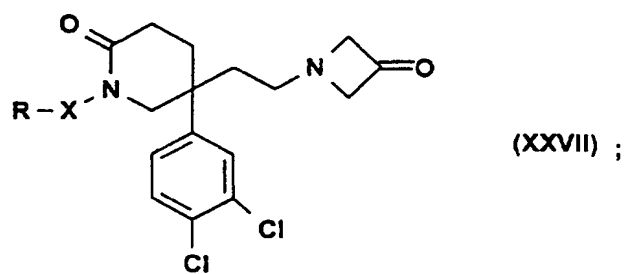


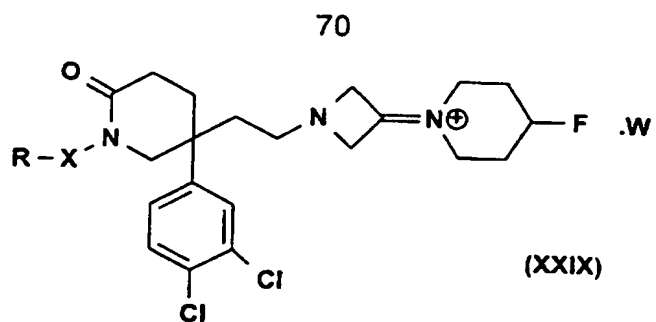
5



10

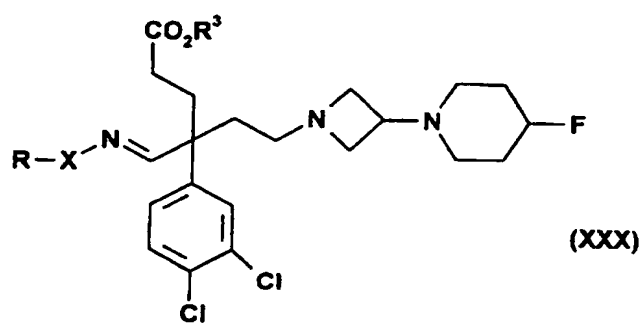
wherein Y⁷ is a leaving group;





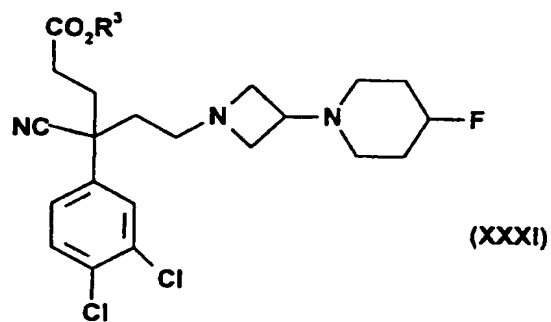
wherein W is an anion;

5



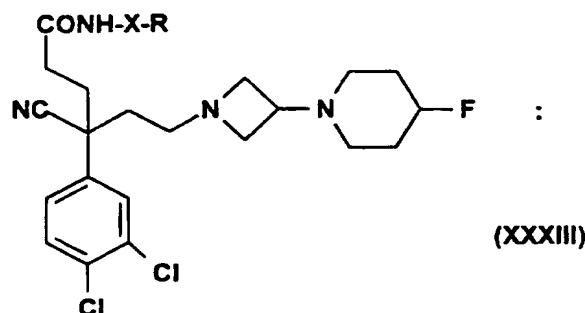
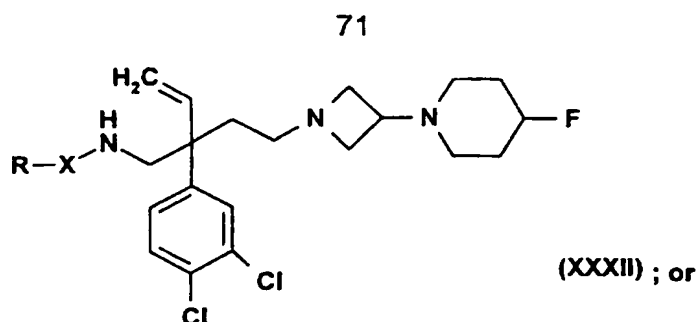
wherein R³ is an ester-forming group;

10



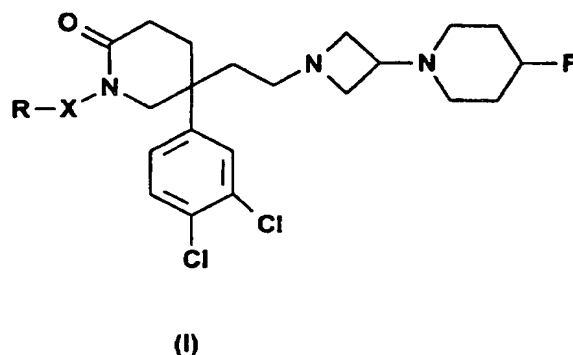
15

wherein R³ is an ester-forming group;



5 wherein R and X are as defined in any of claims 1 to 7.

18. A process for the preparation of a compound of the formula:-



10 or a pharmaceutically acceptable acid addition salt thereof,

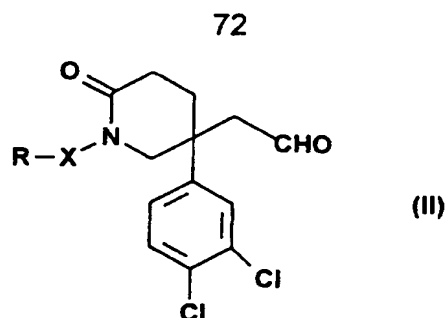
wherein X is a direct link or C₁-C₄ alkylene; and

R is C₃-C₇ cycloalkyl optionally substituted by 1 or 2 substituents
each independently selected from fluoro and C₃-C₇ cycloalkyl:

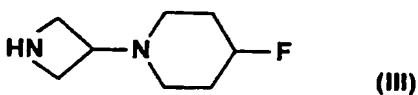
with the proviso that X is not methylene when R is cyclopropyl,

15 which comprises:

(a) reductive amination using as starting materials a compound of the formula:-

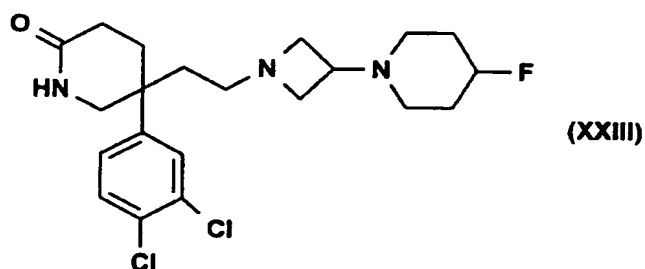


where R and X are as defined for a compound of the formula (I), and a compound of the formula:-

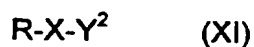


, or an acid addition salt thereof;

(b) alkylation of a N-deprotonated form of a compound of the formula:

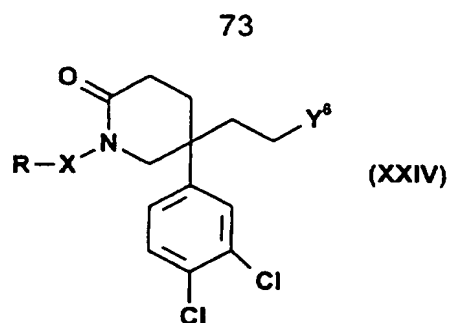


with a compound of the formula:



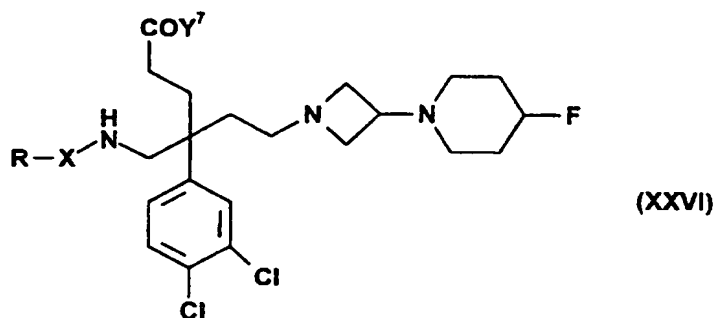
wherein Y^2 is a leaving group and R and X are as defined for a compound of the formula (I);

(c) reaction of a compound of the formula:



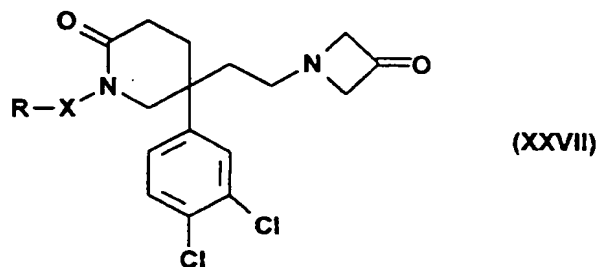
wherein R and X are as defined for a compound of the formula (I) and Y⁶ is a
 5 leaving group with a compound of the formula (III), or an acid addition salt thereof,
 as defined in process (a).

(d) intramolecular cyclisation of a compound of the formula:



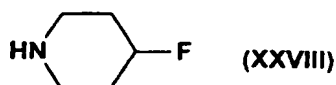
wherein R and X are as defined for a compound of the formula (I) and Y⁷ is a
 leaving group;

(e) reductive amination using as starting materials a compound of the formula:



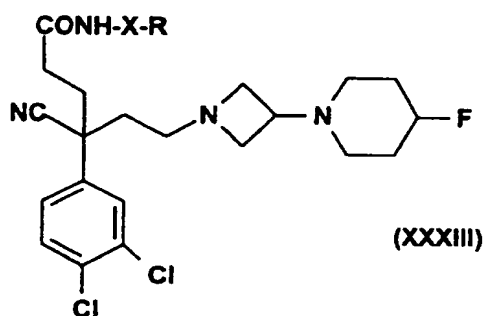
74

wherein R and X are as previously defined for a compound of the formula (I), and
a compound of the formula:



, or an acid addition salt thereof; or

(f) reductive cyclisation of a compound of the formula:



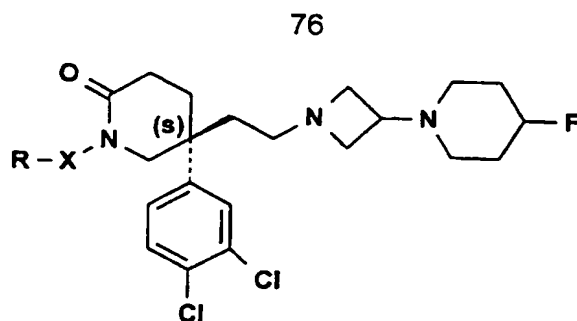
wherein X and R are defined for a compound of the formula (I):

15 any of said processes (a) to (f) being followed by, optionally, conversion of the
compound of the formula (I) to a pharmaceutically acceptable acid addition salt
thereof.

19. A process as claimed in claim 18, part (a), wherein the acid addition salt of
20 the compound of the formula (III) is a para-toluenesulphonate salt.

20. A process as claimed in claim 18, part (a), or 19 wherein an acid acceptor
is present.

21. A process as claimed in any of claims 18, part (a), to 20 wherein the reductive amination is carried out in the presence of sodium triacetoxymethylborohydride.
- 5 22. A process as claimed in any of claims 18, part (a), to 21 wherein tetrahydrofuran is used as a solvent.
23. A process as claimed in any of claims 18, part (a), to 22 wherein the reductive amination is carried out in the presence of acetic acid.
- 10 24. A process as claimed in any of claims 18 to 23 wherein X is a direct link, methylene or ethylene.
- 15 25. A process as claimed in any of claims 18 to 24 wherein X is methylene.
26. A process as claimed in any of claims 18 to 25 wherein R is C₃-C₆ cycloalkyl optionally substituted by 1 or 2 substituents each independently selected from fluoro and cyclopropyl.
- 20 27. A process as claimed in any of claims 18 to 26 wherein R is cyclopropyl, 1-cyclopropylcyclopent-1-yl, cyclohexyl or 4,4-difluorocyclohexyl.
28. A process as claimed in any of claims 18 to 27 wherein R is 4,4-difluorocyclohexyl.
- 25 29. A process as claimed in any of claims 18 to 23 wherein R-X is 4,4-difluorocyclohexylmethyl, cyclohexyl, 1-cyclopropylcyclopent-1-yl or 2-cyclopropylethyl.
- 30 30. A process as claimed in any of claims 18 to 29 which is used to prepare a compound of the formula:



wherein X and R are as defined in claim 18 or any of claims 24 to 29.

- 5 31. A process as claimed in claim 18 or 30 wherein R-X is 4,4-difluorocyclohexylmethyl.
32. A process as claimed in claim 31 wherein the compound of the formula (I) prepared is converted to a pharmaceutically acceptable acid addition salt thereof.
- 10 33. A process as claimed in claim 32 wherein the acid addition salt is the disuccinate salt.
34. A process for the preparation of a pharmaceutical composition which
- 15 comprises combining a compound of the formula (I), or a pharmaceutically acceptable acid addition salt thereof, which has been prepared by process as claimed in any of claims 18 to 33, with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/00162

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/14 A61K31/435 C07D401/04 C07D205/04 C07D211/76

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 96 05193 A (PFIZER LTD) 22 February 1996 cited in the application see page 11; claim 1; example VIII	1-34
P,A	EP 0 723 959 A (SANOFI) 31 July 1996 see the whole document	1-34
A	EP 0 512 901 A (ELF SANOFI) 11 November 1992 see the whole document	1-34

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

18 April 1997

Date of mailing of the international search report

23 -05- 1997

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Gettins, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/00162

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9605193 A	22-02-96	AU 3254995 A BR 9503582 A CA 2197086 A FI 970523 A	07-03-96 30-04-96 22-02-96 07-02-97
EP 723959 A	31-07-96	FR 2729951 A JP 8245622 A	02-08-96 24-09-96
EP 512901 A	11-11-92	FR 2676055 A AU 652046 B AU 1591692 A CA 2067877 A FI 951242 A FI 951243 A JP 5186425 A NO 178573 B NZ 242586 A US 5340822 A	06-11-92 11-08-94 05-11-92 04-11-92 16-03-95 16-03-95 27-07-93 15-01-96 26-10-95 23-08-94